Time trends and long-term outcome of late-life depression

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Time trends and long-term outcome of late-life depression: an epidemiological perspective

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Time trends and long-term outcome of late-life depression: an epidemiological perspective

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copromotoren:	dr. H.C. Comijs
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Chapter 1

General introduction

1.1 Introduction

Whether depression rates are increasing with time is a controversial question and a topic for ongoing debate.[1] Already in 1980, Srole and colleagues challenged claims of a deteriorating mental health in successive generations, which had been postulated by the Mental Paradise Lost doctrine.[2] To date, however, major depressive disorder (MDD) has become the second leading cause of Years Lost to Disability worldwide.[3] Recently, also the importance of investigating trends in milder variants of depression has been stressed,[4] because the so-called subthreshold depression is highly prevalent, associated with poor health outcomes, and a major risk factor for developing major depressive disorder.[5] Another intriguing topic of current scientific debate is whether depression in later life is a chronic, rather than a transient, condition. Detailed information on the long-term outcome of depression is required to answer that question, but studies providing such information are scarce. In this thesis I will provide the results from our epidemiological survey on both time-trends in rates and excess mortality, and the long-term outcome of depression in later life.

1.2 Late-life depression

Depressive disorders are as common in later life as in early life with a prevalence of about 10-15%, of which a quarter is severe. It is believed that depressive symptoms exist on a continuum of severity that includes subthreshold depression, a condition described as a clinically relevant level of depressive symptoms without meeting full diagnostic criteria for a major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases.[6] Both major depressive disorder and subthreshold depression are associated with poor health outcomes, such as a diminished quality of life,[7] decline in physical health,[8] disability,[9] increased health care utilization,[10] and excess mortality.[11] Because of the ongoing increase of the aging population, the number of older persons suffering from depression will further grow in the forthcoming years, and thus will become an even more relevant issue for public health care.

1.3 An epidemiological perspective

Depression epidemiology provides a description of how often depression occurs in populations, the rates at which depression change through time, and the factors that explain depression. Epidemiological studies can provide useful information for public health decisions about the prevention, treatment, and social costs of depression.[12] A useful measure to quantify the occurrence of depression in the population is the prevalence estimate, a ratio describing the number of people with depression in a specific population in a designated time period. The incidence rate refers to new cases of depression during a specific time period occurring in a population initially free of depression. Prevalence, incidence, and mean duration are mathematically related. The prevalence is proportional to incidence times duration. The mean duration of depression is an indicator of its chronicity. Because prevalence rates of depression do not reflect only changes in the number of new cases (incidence), but also the length of time of cases with depression (duration), it is important to measure incidence as well. However, incidence studies are even more scarce than prevalence studies because they are expensive to conduct and time-consuming. Yet, relying solely on prevalence estimates makes it impossible to distinguish developments in the occurrence of new cases from developments in survival, which are both important factors to consider, because developments in one have different public health implications than developments in the other.

An important focus of this thesis is estimating the effects of putative risk and protective factors of depression on the occurrence of depression in the population over time. A risk factor increases the likelihood that a person possessing the factor will develop depression, compared to a person who does not possess the factor. A protective factor decreases the likelihood that a person possessing the factor will develop depression compared to a person who does not possess the factor. The ultimate goal of epidemiology is to elucidate the cause of depression, since targeted treatments and preventive interventions can then be developed to help reduce the burden of depression in the community. Although the identification of risk and protective factors should not be viewed as synonymous with establishing proof of causation, they may provide crucial clues in the search for causes. Since a plausible model accounting for biological and psychosocial risk and protective factors is needed for the interpretation of effect measures, the framework of the dynamic equilibrium model of depression was used in this thesis.

1.4 The Dynamic Equilibrium Model of Depression

Hippocrates held that diseases were caused by imbalances in the four humors (blood, phlegm, yellow bile, black bile), and that melancholia (i.e. depression) was caused by excess black bile. His idea was influential until the 19th century. The current understanding is that the etiology of depression is obviously complex and involves numerous vulnerability factors and interactions between those factors and stress.[13] Models based on this theory are collectively called diathesis-stress models - which also includes the dynamic equilibrium model of depression - and have the potential to understand how vulnerability factors from different domains of functioning may increase susceptibility to depression and subsequently exceed a threshold for the onset of depression.[14]

Audy (1971) suggested that the preservation of health requires the maintenance of a dynamic equilibrium against insults coming from chemical, physical, infectious, psychological and social environmental factors.[14] A disorder occurs when the equilibrium is disturbed by an inability to maintain homeostasis. The dynamic equilibrium model of depression thus assumes that imbalances in multiple risk and protective factors of depression from biological, psychological, and social domains of functioning determine the etiology and onset of depression (Figure 1).[15]

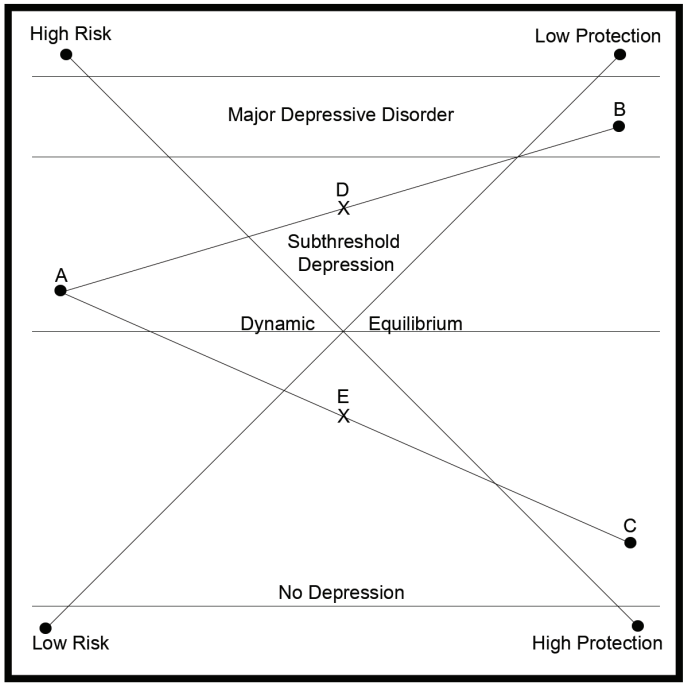

Figure 1. Strong simplification of a dynamic equilibrium between a risk and protection status of depression determining depression outcome. Depression may occur when imbalances exist between the risk and protection status of depression. For example, a moderate risk (A) with low protection (B) may result in subthreshold depression (D), whereas a moderate risk (A) with high protection (C) may not result in depression (E)

1.5 Time-trends in risk and protective factors of depression

The distribution of risk and protective factors for a disease in the population changes over time. Studying time-trends in exposure to risk and protective factors and their role in observed disease trends may improve the understanding of major causes of disease burden and etiology.[16] It has been well established, for example, that the prevalence of cardiovascular disease has declined in recent decades and that this decline can be attributed to a lower exposure to risk factors such as smoking, hypercholesterolemia and high blood pressure.[16,17] Conversely, the prevalence of diabetes mellitus has increased, which has been attributed to an increased exposure to risk factors such as obesity and sedentary lifestyle.[18,19] To our knowledge, no previous study systematically addressed time-trends in the exposure to risk and protective factors of depression and their role in observed time trends in depression rates.

1.6 Time-trends in excess mortality of depression

Subthreshold depression and major depressive disorder are both associated with premature mortality,[11,20] but little is known whether excess mortality rates of depression have changed over time. A body of evidence support the hypothesis that premature mortality in late-life depression has been largely due to mortality from cardiovascular disease (CVD).[21–24] Since premature mortality from cardiovascular disease has decreased substantially in recent decades,[25,26] excess mortality of depression may also have declined in recent decades. However, this remains to be explored.

1.7 Long-term outcome of depression

An unfavorable outcome of late-life depression has been demonstrated in both community samples,[27–30] and clinical samples.[31–36] Beekman et al. (2002) studied the six-year course of community-dwelling older adults with late-life depression, using both diagnostic interviews and self-reports, and found that 32% had a severe chronic course and 44% an unfavorable but fluctuating course, whereas only 23% showed remission.[28] More studies on the long-term prognosis of late-life depression are required to inform both health policy makers and clinicians. Also factors can be identified that are associated with a poor outcome, which may contribute to the improvement of prevention and treatment strategies.

1.8 Research Questions of the Thesis

1. To what extent are secular trends in the exposure to risk and protective factors of depression associated with secular trends in the prevalence of depression? (Chapter 2)
2. To what extent can birth-cohort differences in the incidence of depression be identified and explained? (Chapter 3)
3. To what extent can secular trends in excess mortality of late-life depression be identified and explained? (Chapter 4)
4. What is the long-term outcome of subthreshold depression in later life, and what are predictors of major depressive disorder and recovery? (Chapter 5)
5. What is the long-term prognosis of late-life depression in terms of attrition and course among clinically depressed patients? (Chapter 6)

1.9 Studies used in this thesis

Longitudinal Aging Study Amsterdam (LASA)

Data was predominantly used from the Longitudinal Aging Study Amsterdam (LASA), an ongoing prospective population-based-study in the Netherlands.[37,38] In short, in 1992/93 a first cohort (N=3,107, birth years 1908-1937) was recruited from the population registries of eleven municipalities in three geographic areas of the Netherlands including a random sample of 55-85-year-old men and women, stratified by age and sex according to the expected five-year mortality. The cooperation rate of this first cohort was 62%. Follow-ups were conducted in 1995/96 (N=2,545), 1998/99 (N=2,076), and 2001/02 (N=1,691). In 2002/03 and 2012/13, a second (N=1,002, birth years 1938-1947) and third cohort (N=1.023, birth years 1948-1957) were recruited, respectively, both including a random sample of 55-64-year-olds selected from the same sampling frame and measured identically to the first cohort. The cooperation rates were 62% and 63% for the second and third cohort, respectively. In subsequent observational cycles, respondents from the second and third cohort were combined with those from the first cohort. To date, follow-ups were conducted in 2005/06 (N=2,165), 2008/09 (N=1,818), and 2011/12 (N=1,522).

Netherlands Study of Depression in Older persons (NESDO)

The Netherlands Study of Depression in Older persons (NESDO) is a multi-site prospective cohort study designed to examine the course and consequences of depressive disorders in older adults.[39] In short, data collection of the baseline measurement took place between 2007 and 2010. At baseline, NESDO included 378 depressed patients, having major depressive disorder, dysthymia or minor depression according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR criteria),[40] and 132 non-depressed controls, aged

≥ 60 years.[35] Depressed patients were recruited in five regions in the Netherlands from both mental health care facilities and general practitioners. Non-depressed controls were recruited from general practitioners and were included if they had no lifetime diagnosis of depression. Follow-up assessments by means of a face-to-face interview were performed two-years,[35] and six-years after baseline using the same measurement instruments as at baseline. Additionally, postal assessments were performed every six-months.

1.10 Outline of the Thesis

In **chapter two** we first hypothesize that the prevalence of MDD remains stable due to a balance in risk and protective factors. Second, in contrast to MDD, we hypothesize that the prevalence of SUBD will fluctuate more according to secular trends in psychosocial circumstances.

In **chapter three** we hypothesize to find a higher incidence of depression in the recent cohort compared to the early cohort and that this increase in incidence rate could be explained by higher average levels of health-related risk factors in the recent cohort, as compared to the earlier cohort.

In **chapter four** we hypothesize that there is a downward trend in excess mortality of late-life depression, in particular among men, which can be explained by a decrease in cardiovascular mortality.

In **chapter five** we hypothesize that a substantial group of older adults with SUBD has short-lived and self-limiting symptoms, likely to be determined by concurrent psychosocial circumstances (stress related); and those more at risk of developing MDD are more likely to exhibit longstanding vulnerability for mood disorders.

In **chapter six** it was hypothesized that the long-term prognosis of late-life depression is poor, with a high mortality rate and an unfavorable course, including recurrence and chronicity, in most patients.

In **chapter seven** results will be summarized and overall (public health and clinical) implications will be discussed.

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Chapter 2

Secular trends in the prevalence of major and subthreshold depression among 55-64-year-olds over twenty years

Psychological Medicine 2018 Aug;48(11):1824-1834

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Aartjan Beekman

Abstract

Objective: Studying secular trends in the exposure to risk and protective factors of depression and whether these trends are associated with secular trends in the prevalence of depression is important to estimate future healthcare demands and to identify targets for prevention.

Method: Three birth cohorts of 55-64-year-olds from the population-based Longitudinal Aging Study Amsterdam were examined using identical methods in 1992 (n=944), 2002 (n=964) and 2012 (n=957). A two-stage screening design was used to identify subthreshold depression (SUBD) and major depressive disorder (MDD). Multinomial Logistic Regression analyses were used to identify secular trends in depression prevalence and to identify factors from biopsychosocial domains of functioning that were associated with these trends.

Results: Compared with 1992, MDD became more prevalent in 2002 (OR: 1.90, 95%-CI: 1.10-3.28, p=0.022) and 2012 (OR: 1.80, 95%-CI: 1.03-3.14, p=0.039). This was largely attributable to an increase in the prevalence of chronic diseases and functional limitations. Socioeconomic and psychosocial improvements, including an increase in labor market participation, social support and mastery, hampered MDD-rates to rise more and were also associated with a 32% decline of SUBD-rates in 2012 as compared to 2002 (OR: 0.68, 95% CI: 0.48-0.96, p=0.03).

Conclusions: Among late middle-aged adults, there is a substantial net increase of MDD, which is associated with deteriorating physical health. If morbidity and disability continue to increase, a further expansion of MDD-rates may be expected. Improving socioeconomic and psychosocial conditions may benefit public health, as these factors were protective against a higher prevalence of both MDD and SUBD.

Introduction

The distribution of risk and protective factors for disease in the population changes over time. Studying secular trends in exposure to risk and protective factors and their role in observed disease trends may improve the understanding of major causes of disease burden.[1] It has been well established, for example, that the prevalence of cardiovascular disease has declined in recent decades and that this decline can be attributed to a lower exposure to risk factors such as smoking, hypercholesterolemia and high blood pressure.[1,2] Conversely, the prevalence of diabetes mellitus has increased, which has been attributed to an increased exposure to risk factors such as obesity and sedentary lifestyle.[3,4] Since major depressive disorder (MDD) is the second leading cause of Years Lost to Disability (YLD) worldwide,[5] studying secular trends in depression prevalence is of great importance to estimate future healthcare demands and to identify targets for prevention.

Although the majority of available studies suggest that MDD rates have increased in the last decades;[6–11] other studies have shown contrasting results.[12–17] A recent study has stressed the importance of investigating trends in milder depression too, because subthreshold depression (SUBD) was more prevalent among later-born birth cohorts.[18] Evidence is growing that SUBD is also an important determinant of public health and a major risk factor for MDD.[19] The topic on secular trends in depression prevalence has been one of ongoing controversy, since it has been questioned whether observed increases in depression rates constitutes 'true' increases or have been the result of changes in diagnostic criteria and differences in assessment methods.[15,20] Moreover, it is not known what factors have contributed to secular trends in depression prevalence.

MDD is preeminently a multifactorial disease, which is determined by an interaction of biological, psychological and social factors according to the biopsychosocial model.[21] The heritability of MDD has been estimated at 37%,[22] implying that non-genetic factors explain an important part of the etiology of MDD. It has been suggested that SUBD is determined even more by non-genetic factors than MDD.[23] This non-genetic influence may best be illustrated by a dynamic equilibrium of multiple interacting risk and protective factors (Figure 1).[24] For some known risk factors of depression the exposure has declined in recent decades, such as smoking and cardiovascular disease;[2,25] whereas the exposure to other known risk factors has increased, including diabetes mellitus,[4] chronic diseases,[26] excessive alcohol consumption,[27] and lack of social support.[28] For some known protective factors of depression the exposure has increased, including educational level,[29] socioeconomic advantages,[30] and management of depression;[17] while exposure to religiousness has decreased.[31] An ambiguous effect has been described for the dramatic shift in dual family and work roles for women after World War II.[32] This dual role may entail both a risk and protective factor, due to higher

stress levels and meaningful engagement in life, respectively.[33] Whether the prevalence of MDD and SUBD has been influenced by secular trends in risk and protective factors for depression has not been studied yet.

In order to identify secular trends properly, it is important to select a study population with an age range that likely has undergone the greatest change in risk and protective factors in the last few decades and to use consistent diagnostic criteria across cohorts.[34] Moreover, from a clinical point of view, the study population should be a suitable target for prevention. We assumed that 55-64-year-olds were most appropriate for this purpose, because this group is young enough to experience secular trends in psychosocial circumstances, such as dual roles, and old enough to experience secular trends in the occurrence of health problems, such as somatic diseases and disability.

The aim of the present paper is to explore whether and to what extent a dynamic equilibrium of multiple risk and protective factors is associated with depression outcome over two decades among three population-based cohorts of 55-64-year-olds in the Netherlands. First, we hypothesize that the prevalence of MDD remains stable due to a balance in risk and protective factors. Second, in contrast to MDD, we hypothesize that the prevalence of SUBD will fluctuate more according to secular trends in psychosocial circumstances.

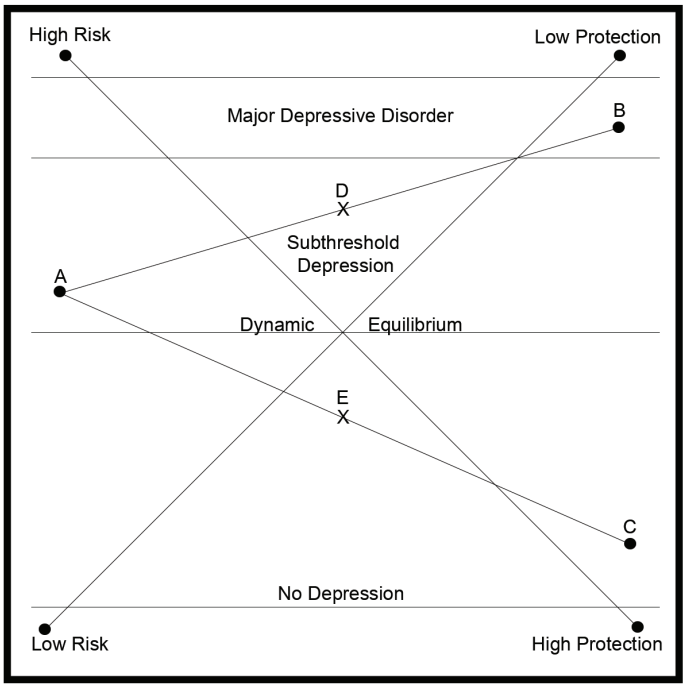

Figure 1. Strong simplification of a dynamic equilibrium between multiple risk and protective factors determining major and subthreshold depression. For example, a moderate risk (A) with low protection (B) may result in subthreshold depression (D), whereas a moderate risk (A) with high protection (C) may not result in depression (E)

Methods

Study sample

Data were used from the Longitudinal Aging Study Amsterdam (LASA), an ongoing prospective population-based-study in the Netherlands. Sampling procedures have been previously described.[35,36] In short, in 1992/93 the first cohort (N=3,107, birth years 1908-1937) was recruited from the population registries of eleven municipalities in three geographic areas of the Netherlands including a random sample of 55-85-year-old men and women, stratified by age and sex according to the expected five-year mortality. The cooperation rate of the first cohort was 62%, also for the 55-64-year-olds subsample. In 2002/03 and 2012/13, a second (N=1,002, birth years 1938-1947) and third cohort (N=1,023, birth years 1948-1957) were recruited, respectively, both including a random sample of 55-64-year-olds selected from the same sampling frame and measured identically to the first cohort. The cooperation rates were 62% and 63% for the second and third cohort, respectively. All interviews were conducted in the homes of the respondents by trained and supervised interviewers.

The present study involved a cohort comparison of both depression outcome and the exposure to risk and protective factors covering twenty years of time. A strict age limit of 55-64-years was applied resulting in the inclusion of N=2,951 respondents (N=964 from the first, N=996 from the second and N=991 from the third cohort). Subsequently, N=86 respondents were excluded (N=20 from the first, N=32 from the second, and N=34 from the third cohort) due to missing data on depression outcome leaving a total sample of N=2,865 respondents, including N=944 in the first, N=964 in the second and N=957 in the third cohort. Written informed consent was obtained from all respondents. The Ethical Review Board of the VU University Medical Center approved the study.

Dependent variable

A two-stage-screening design was used to identify SUBD and MDD as follows. First, the Center for Epidemiological Studies Depression Scale (CES-D) was applied to identify respondents with clinically relevant depression (cut-off score CES-D ≥ 16).[37] The psychometric properties of the CES-D were found to be good.[38] Second, in respondents who screened positive in the first stage (CES-D ≥ 16), the Diagnostic Interview Schedule (DIS) was scheduled 2-8 weeks after the CES-D interview.[39] Depression outcome was defined as a variable containing three categories. Respondents without clinically relevant depression (CES-D < 16) were indicated as having no depression. Respondents with clinically relevant depression (CES-D ≥ 16) but without a past-year diagnosis of MDD according to the DIS were indicated as having SUBD. Respondents with clinically relevant depression (CES-D ≥ 16) and also a past-year diagnosis of MDD were indicated as having MDD.

Main independent variable

The 'cohort' variable was categorized into three groups; we refer to these cohorts as the 'early cohort' (1992/93), 'middle cohort' (2002/03) and 'recent cohort' (2012/13).

Explanatory independent variables

Based on two literature reviews among community-dwelling older adults aged 55 years or older,[40,41] putative risk and protective factors were included from biological, psychological and social domains of functioning. According to the literature and based on biological plausibility, factors were considered either a risk or protective factor.

The following risk factors were included. *Urbanicity* was dichotomized according to the postal code density in 'city' (>1000 addresses/km^2) versus 'rural' (<1000 addresses/km^2).[42] The *number of chronic diseases* was assessed by self-report on current diseases and included cardiovascular disease, diabetes mellitus, cancer, cerebrovascular accident, arthritis and chronic-obstructive-pulmonary-disease (COPD) (range, 0-7).[43] *Functional limitations* were measured by self-report and dichotomized in 'none' versus 'one or more' limitations.[44] *Body mass index* was calculated as measured body weight (kg) divided by measured height (m^2). *Pain* was measured with the Nottingham Pain Profile scale (range, 5-10).[45] *Sleep problems* were measured with a four-item self-questionnaire (range, 3-12).[45] *Alcohol consumption* was measured by the number of alcohol units consumed per day (u/d) and categorized into: abstainer (0 u/d), moderate (men, 1-3 u/d; women, 1-2 u/d) and excessive (men, ≥4 u/d; women, ≥3 u/d).[46] *Smoking* was dichotomized into 'current smoker or stopped ≤ 15 years ago' versus 'never smoked or stopped > 15 years'.[47] *Physical activity* was measured by calculating the total time in minutes per day spent on physical activity.[48] *Neuroticism* was measured with a 25-items subset from the 36-item Dutch Personality Questionnaire (range, 0-50).[49] *Loneliness* was assessed with the De Jong-Gierveld Loneliness Scale (range, 0-11).[50]

The following protective factors were included. *Religiousness* was dichotomized in having a religion or not. *Partner status* was dichotomized in having a partner in or outside the household versus no partner. *Education* was based on the number of years of education (range, 5-18). *Labor market participation* was assessed by self-report. *Physical performance* was measured with three performance tests (range, 0-12).[51] *General cognitive functioning* was measured with the Mini Mental State Examination (range, 0-30).[52] *Mastery* was measured with a translated and abbreviated Dutch version of the Pearlin Mastery Scale (range, 5-25).[53] *Personal network size* was based on the total number of network members (range, 0-75); and the *exchange of social support* (both instrumental and emotional) was collected for nine network members whom the respondent had the most frequent contact with (range, 0-36).[54]

Use of *antidepressants* and *benzodiazepines* were assessed by directly recording the medication from drug containers in the home of the respondents.[55] All scales were either previously validated in comparable samples in the Netherlands or in LASA pilot studies.[56] Because the dataset contained more than 5% missing values in some risk and protective factors, Multiple Imputation (MI) was performed, including 25 imputations and 50 iterations.

Statistical analyses

Descriptive statistics were performed on complete-cases data and weighted according to the distribution of age and sex in the recent cohort. This was done to make sure that changes in the prevalence of depression reflected secular trends and were not due to distributional differences in age and sex. All risk and protective factors were separately investigated for its explanatory ability. Chi-square and *t* tests were performed to examine the association between each factor with both 'cohort' and 'depression outcome'. For this preliminary exploration, a liberal p-level < 0.30 was used so as not to miss important explanatory factors.[57] Factors associated with both 'cohort' (Table 1) and 'depression outcome' (eTable 1, supplemental) were considered as potential explanatory factors.

Further analyses performed with Multinomial Logistic Regression were not weighted since all models were standard adjusted for age and sex. A basic model was created to test the association between 'cohort' and 'depression outcome', adjusted for age and sex, to estimate the degree of secular trends in the prevalence of MDD and SUBD. The middle and recent cohorts were compared to the early cohort (=reference) and an additional comparison was made between the recent and the middle cohort (=reference). Subsequently, potential explanatory factors were manually entered one by one into the basic model and the % change in odds ratio of 'cohort' (OR_{cohort}) was estimated for MDD (Table 2) and SUBD (Table 3). The % change in (OR_{cohort}) was calculated with following formulas: if OR > 1: (($OR_{model\ x} - OR_{basic\ model}$)/ ($OR_{basic\ model}$ -1) x 100); if OR < 1: (($OR_{basic\ model} - OR_{model\ x}$)/ ($OR_{basic\ model}$ -1) x 100).[58]

Factors were considered to be explanatory when two conditions were met after entering the basic model: first the magnitude of the association (OR_{cohort}) was reduced: thus decrease in OR if OR>1 or increase in OR if OR<1, accompanied by a decrease in P value, and second the % change (OR_{cohort}) was ≥ 10%. Factors were considered to be suppressors when the opposite was observed: first the magnitude of the association (OR_{cohort}) became stronger: thus decrease in OR if OR<1 or increase in OR if OR>1, accompanied by an increase in P value, and second the % change (OR_{cohort}) was ≥ 10%.[59] Finally, multivariable analyses were performed to estimate the total percentage that could be explained by adjusting the basic model subsequently for the overall influence of suppressors, the overall influence of explanatory factors and finally for psychotropic medication (Table 4). Data-analyses were conducted with SPSS v22 and Stata v12.

Results

Table 1 shows the past-year prevalence of MDD in 1992, 2002 and 2012, which was 2.1%, 3.9% and 3.8% respectively. The point prevalence of SUBD in 1992, 2002 and 2012 was 7.2%, 8.7% and 6.2% respectively. There is an increase in the use of antidepressants in successive cohorts. The use of benzodiazepines declined in the recent cohort. Also shown in Table 1 are the secular trends in the exposure to risk and protective factors.

Secular trends in the exposure to risk and protective factors
It can be seen that among the risk factors: chronic diseases, functional limitations, diabetes, cancer, and arthritis are more prevalent in successive cohorts; whereas the prevalence of cardiovascular disease, smoking, physical activity, neuroticism and loneliness has decreased. Among the protective factors: successive cohorts have an increase in the exposure to educational level, labor market participation, cognitive functioning, mastery and exchange of social support; while the exposure to religiousness and physical performance has decreased. The exposure to other factors, such as CVA, COPD, pain, sleep problems, alcohol consumption and network size, fluctuated between cohorts.

Secular trends in MDD prevalence and explanatory factors
The prevalence of MDD in both the middle cohort (OR: 1.90, 95% CI: 1.10-3.28, p=0.022) and recent cohort (OR: 1.80, 95% CI: 1.03-3.14, p=0.039) is higher as compared to the early cohort (Table 2). However, compared to the middle cohort, the prevalence of MDD remained stable (OR: 0.95, 95% CI: 0.60-1.51, p=0.82). Subsequently, the potential explanatory and suppressor effect of each factor is shown in Table 2. The number of chronic diseases, functional limitations, arthritis and COPD were found to have an explanatory ability in both the middle and recent cohort. Additionally, pain and sleep problems were only associated with the increase in MDD rates in the middle cohort.

Several factors suppressed the relationship between 'cohort' and 'MDD outcome'. Common factors for both cohorts are neuroticism, labor market participation, physical performance, mastery and emotional support given. In addition, only in the recent cohort suppressor effects are also seen for cardiovascular disease, smoking, loneliness, educational level, network size, instrumental support given and emotional support received. After adjustment for all suppressors the (OR_{cohort}) increased 1.2 times in the middle and 2.4 times in the recent cohort (Table 4). This can be understood as follows: if the prevalence of the suppressor factors had been stable over time, the prevalence of MDD would have been even much higher. Table 4 shows the overall influence of suppression and explanatory effects. The increase in the prevalence of health problems partly explained (24%) the rise in MDD rates. The use of antidepressants had an additional explanatory effect.

Secular trends in SUBD prevalence and explanatory factors

The prevalence of SUBD in the middle (OR: 1.29, 95% CI: 0.92-1.80, p=0.143) and recent cohort (OR: 0.87, 95% CI: 0.61-1.26, p=0.471) as compared to the early cohort remained stable. The SUBD prevalence found in the recent cohort was lower (OR: 0.68, 95% CI: 0.48-0.96, p=0.03) as compared to the middle cohort (Table 3). This decline in SUBD rates was not suppressed and could entirely be explained by both the overall effect of a decrease in prevalence of risk factors (BMI, pain, sleep problems, smoking, neuroticism and loneliness) and by an increase in the prevalence of protective factors (educational level, labor market participation, mastery and network size). Use of benzodiazepines had no additional explanatory effect (Table 4).

Table 1. Sample characteristics and secular trends in the exposure to risk and protective factors

	Early cohort 1992 (n = 944)	Middle cohort 2002 (n = 964)	Recent cohort 2012 (n = 957)	P Value
Female, No. (%)	486 (51.5)	502 (52.1)	492 (51.4)	0.950
Age, 55-64, mean (SD), y	60.2 (2.8)	59.9 (2.9)	60.2 (2.8)	**0.044**
Risk factors				
Lives in city, No. (%)	535 (56.6)	556 (57.7)	575 (60.1)	0.290
# Chronic diseases, 0-7, median (IQR)	0.0 (1.0)	1.0 (1.0)	1.0 (1.0)	**<0.001**
≥1 Functional limitations, No. (%)	164 (17.4)	258 (26.8)	262 (27.4)	**<0.001**
Cardiovascular disease, No. (%)	155 (16.4)	141 (14.6)	118 (12.3)	**0.039**
Diabetes, No. (%)	32 (3.4)	67 (7.0)	79 (8.3)	**<0.001**
Cancer, No. (%)	57 (6.0)	83 (8.6)	92 (9.6)	**0.013**
CVA, No. (%)	18 (1.9)	27 (2.8)	18 (1.9)	0.296
Arthritis, No. (%)	263 (27.9)	328 (34.1)	374 (39.1)	**<0.001**
COPD, No. (%)	70 (7.4)	98 (10.2)	96 (10.0)	0.065
Body Mass Index, median (IQR)	26.4 (4.4)	27.0 (5.3)	26.7 (5.7)	**0.005**
Pain, 5-10, median (IQR)	5.0 (0.0)	5.0 (1.0)	5.0 (1.0)	**0.018**
Sleep problems, 3-12, mean (SD)	5.6 (2.1)	5.7 (2.2)	5.8 (2.0)	0.149
Alcohol consumption, No. (%)				**<0.001**
None	128 (14.8)	72 (8.0)	114 (13.4)	
Moderate	634 (73.5)	651 (72.0)	600 (70.8)	
Excessive	102 (11.6)	181 (20.0)	134 (15.8)	
Smoking, No. (%)	442 (51.1)	421 (46.6)	304 (35.8)	**<0.001**
Physical activity, min/day, median (IQR)	170.2 (158.6)	143.6 (133.9)	132.9 (124.1)	**<0.001**
Neuroticism, 0-50, median (IQR)	4.0 (7.0)	4.0 (6.0)	2.0 (6.0)	**<0.001**
Loneliness, 0-11, median (IQR)	1.0 (2.0)	1.0 (2.0)	0.0 (2.0)	**0.015**
Protective factors				
Religious, No. (%)	556 (58.9)	500 (51.9)	427 (44.6)	**<0.001**
Partner, No. (%)	785 (83.2)	812 (84.2)	780 (81.5)	0.277
Educational level, 5-18, mean (SD), y	9.5 (3.3)	10.4 (3.4)	11.7 (3.4)	**<0.001**
Labor market participation, No. (%)	277 (29.8)	410 (42.6)	606 (63.3)	**<0.001**
Physical performance, 0-12, mean (SD)	8.6 (2.5)	8.9 (2.4)	9.1 (2.1)	**<0.001**
Cognitive functioning, 0-30, median (IQR)	28.0 (2.0)	28.0 (2.0)	29.0 (2.0)	**0.001**
Mastery, 5-25, mean (SD)	18.0 (3.3)	18.2 (3.5)	18.8 (3.1)	**<0.001**
Network size, 0-75, median (IQR)	14.0 (11.0)	13.0 (11.0)	19.0 (16.0)	**<0.001**

Table 1. Continued

	Early cohort 1992 (n = 944)	Middle cohort 2002 (n = 964)	Recent cohort 2012 (n = 957)	P Value
Protective factors (Continued)				
Exchange of social support, 0-36, mean (SD)				
Instrumental support given	15.8 (7.0)	17.0 (7.0)	17.8 (6.5)	**<0.001**
Instrumental support received	14.3 (6.4)	14.7 (6.4)	15.4 (5.8)	**<0.001**
Emotional support given	21.3 (8.0)	23.8 (7.7)	24.8 (6.8)	**<0.001**
Emotional support received	22.6 (7.7)	22.4 (7.9)	23.5 (7.0)	**0.004**
Antidepressants use, No. (%)	11 (1.3)	36 (4.0)	60 (7.1)	**<0.001**
Benzodiazepines use, No. (%)	65 (7.5)	69 (7.6)	37 (4.4)	**0.008**
Depression status, No. (%)				**0.029**
No depression	856 (90.7)	843 (87.4)	862 (90.1)	
Subthreshold depression	68 (7.2)	84 (8.7)	59 (6.2)	
Major depressive disorder	20 (2.1)	38 (3.9)	36 (3.8)	

Chi-square values have been computed for categorical variables and t-values for interval variables. Independent-Samples Kruskal-Wallis Tests were used for non-parametric variables
#, number of; SD, standard deviation; IQR, interquartile range

Table 2. Factors associated with an increase in prevalence of major depressive disorder among 55-64-year olds in 2002 and 2012 compared to 1992

Basic model (adjusted for age and sex)
↑ **Exposure to risk factors (explanatory factors)**
Lives in city
Chronic diseases
≥1 Functional limitations
Diabetes
Cancer
CVA
Arthritis
COPD
Body Mass Index
Pain
Sleep problems
Alcohol consumption
Overall effect [a]
↓ **Exposure to risk factors (suppressor factors)**
Cardiovascular disease
Smoking
Neuroticism
Loneliness
Overall effect [a]
↑ **Exposure to protective factors (suppressor factors)**
Educational level
Labor market participation
Physical performance
Cognitive functioning
Mastery
Network size
Exchange of social support
Instrumental support given
Emotional support given
Emotional support received
Overall effect [a]

Middle cohort (vs. early cohort)				Recent cohort (vs. early cohort)			
OR_{Cohort}	OR_{Change}, %	95% CI	P_{Value}	OR_{Cohort}	OR_{Change}, %	95% CI	P_{Value}
1.90		1.10-3.28	**0.022**	1.80		1.03-3.14	**0.039**
1.89	-1	1.10-3.27	**0.022**	1.77	-4	1.01-3.09	**0.045**
1.74	-18	1.00-3.01	**0.049**	1.61	-24	0.92-2.80	0.095
1.61	-32	0.93-2.79	0.089	1.57	-29	0.90-2.74	0.116
1.84	-7	1.06-3.19	**0.029**	1.73	-9	0.98-3.03	0.058
1.89	-1	1.09-3.28	**0.023**	1.79	-1	1.03-3.14	**0.041**
1.86	-4	1.08-3.23	**0.027**	1.80	0	1.03-3.13	**0.039**
1.83	-8	1.06-3.16	**0.029**	1.68	-15	0.97-2.91	0.065
1.81	-10	1.05-3.14	**0.034**	1.72	-10	0.98-2.99	0.057
1.83	-8	1.04-3.21	**0.035**	1.87	+9	1.06-3.30	**0.031**
1.66	-27	0.93-2.96	0.088	1.76	-5	0.97-3.19	0.061
1.75	-17	0.98-3.13	0.061	1.78	-3	0.98-3.24	0.058
1.84	-7	1.07-3.19	**0.028**	1.79	-1	1.03-3.13	**0.040**
1.51	-43	0.81-2.84	0.196	1.58	-28	0.84-2.95	0.153
1.93	+3	1.11-3.35	**0.019**	1.88	+10	1.07-3.31	**0.028**
1.90	0	1.10-3.29	**0.022**	2.06	+33	1.16-3.64	**0.014**
2.01	+12	1.11-3.63	**0.021**	2.89	+136	1.56-5.37	**0.001**
1.98	+9	1.14-3.45	**0.016**	2.08	+35	1.18-3.66	**0.011**
2.12	+24	1.16-3.87	**0.014**	3.40	+200	1.78-6.50	**<0.001**
1.94	+4	1.09-3.44	**0.023**	1.90	+13	1.02-3.55	**0.045**
2.16	+29	1.24-3.78	**0.007**	2.77	+120	1.50-5.11	**0.001**
2.02	+13	1.16-3.52	**0.013**	1.88	+10	1.06-3.35	**0.031**
1.91	+1	1.10-3.31	**0.021**	1.86	+8	1.05-3.29	**0.033**
2.36	+51	1.27-4.37	**0.009**	2.85	+131	1.52-5.36	**0.001**
1.91	+1	1.11-3.31	**0.020**	2.25	+56	1.28-3.96	**0.005**
1.97	+8	1.14-3.41	**0.015**	1.93	+16	1.10-3.38	**0.023**
2.13	+26	1.21-3.77	**0.008**	2.17	+46	1.22-3.86	**0.008**
1.94	+4	1.12-3.35	**0.017**	1.94	+18	1.11-3.42	**0.021**
2.39	+54	1.26-4.56	**0.008**	3.55	+219	1.73-7.25	**0.001**

Table 2. Continued

↓ Exposure to protective factors (explanatory factors)	
Religious	
Partner	
Overall effect [a]	
Psychotropic medication	
Antidepressants use	
Benzodiazepines use	

OR, odds ratio; all factors were manually entered one by one into the basic model and the % change in OR_{Cohort} was estimated (OR_{Change}); [a] multivariable analyses were performed to estimate the cumulative effect within groups

Table 3. Factors associated with a decrease in prevalence of subthreshold depression in 2012 compared to 2002

	Recent cohort (vs. middle cohort)			
	OR_{Cohort}	OR_{Change}, %	95% CI	P_{Value}
Basic model (adjusted age and sex)	0.68		0.48-0.96	**0.030**
↑ Exposure to risk factors (suppressor factors)				
Lives in city	0.67	-3	0.48-0.96	**0.027**
# Chronic diseases	0.67	-3	0.47-0.95	**0.024**
≥1 Functional limitations	0.67	-3	0.47-0.96	**0.030**
Diabetes	0.67	-3	0.47-0.95	**0.024**
Cancer	0.68	0	0.48-0.96	**0.030**
Arthritis	0.66	-6	0.47-0.94	**0.023**
Overall effect [a]	0.67	-3	0.47-0.96	**0.029**
↓ Exposure to risk factors (explanatory factors)				
Cardiovascular disease	0.69	+3	0.49-0.98	**0.039**
CVA	0.69	+3	0.48-0.97	**0.035**
COPD	0.68	0	0.48-0.97	**0.032**
Body Mass Index	0.74	+19	0.52-1.06	0.099
Pain	0.78	+31	0.54-1.11	0.165
Sleep problems	0.74	+19	0.52-1.06	0.100
Alcohol consumption	0.70	+6	0.49-0.99	**0.046**
Smoking	0.76	+25	0.53-1.08	0.126
Neuroticism	0.98	+94	0.68-1.41	0.900
Loneliness	0.74	+19	0.52-1.06	0.096
Overall effect [a]	1.00	+100	0.67-1.49	0.996

Middle cohort (vs. early cohort)				Recent cohort (vs. early cohort)			
OR_{Cohort}	OR_{Change}, %	95% CI	P_{Value}	OR_{Cohort}	OR_{Change}, %	95% CI	P_{Value}
1.89	-1	1.09-3.26	**0.023**	1.78	-3	1.01-3.12	**0.044**
1.96	+7	1.12-3.42	**0.018**	1.74	-8	0.99-3.04	0.054
1.98	+9	1.13-3.46	**0.017**	1.75	-6	0.99-3.09	0.053
1.68	-24	0.95-2.96	0.075	1.41	-49	0.77-2.58	0.267
1.87	-3	1.07-3.25	**0.028**	2.21	+51	1.25-3.91	**0.006**

Table 3. Continued

	Recent cohort (vs. middle cohort)			
	OR_{Cohort}	OR_{Change}, %	95% CI	P_{Value}
↑ Exposure to protective factors (explanatory factors)				
Educational level	0.73	+16	0.51-1.04	0.079
Labor market participation	0.76	+25	0.53-1.10	0.144
Physical performance	0.71	+9	0.50-1.02	0.064
Cognitive functioning	0.71	+9	0.50-1.00	0.050
Mastery	0.78	+31	0.55-1.11	0.169
Network size	0.83	+47	0.58-1.18	0.289
Exchange of social support				
Instrumental support given	0.69	+3	0.49-0.98	**0.040**
Emotional support given	0.70	+6	0.49-0.99	**0.044**
Emotional support received	0.70	+6	0.49-0.99	**0.044**
Overall effect [a]	1.07	+122 [b]	0.74-1.56	0.717
↓ Exposure to protective factors (suppressor factors)				
Religious	0.66	-6	0.47-0.94	**0.022**
Partner	0.66	-6	0.46-0.94	**0.020**
Overall effect [a]	0.65	-9	0.45-0.92	**0.015**
Psychotropic medication				
Antidepressants	0.70	+6	0.49-0.99	**0.044**
Benzodiazepines	0.75	+22	0.53-1.07	0.117

OR, odds ratio; all factors were manually entered one by one into the basic model and the % change in OR_{Cohort} was estimated (OR_{Change}); [a] multivariable analyses were performed to estimate the cumulative effect within groups; [b] read (OR_{Change}) of 122% as 100%

Table 4. Multivariable analyses secular trends in prevalence of MDD and SUBD

	MDD in 2002 (vs. MDD in 1992)		
Model	OR_{Cohort}	OR_{Change}, %	95% CI
I. Basic model (adjusted for age and sex)	**1.90**		**1.10,3.28**
II. Model I + suppressor factors	**2.29**	Ref	**1.19,4.42**
III. Model II + explanatory factors	1.98	-24	0.99,3.93
IV. Model III + antidepressants	1.86	-33	0.91,3.80
V. Model III + benzodiazepines			

OR, odds ratio; bold = significant (95% CI does not include 1); Ref = reference OR to calculate % change
Multivariable analyses estimated the total percentage that could be explained by subsequently adjusting the basic model (Model I) for the cumulative suppression effect (Model II) and cumulative explanatory effect (Model III). MDD models were adjusted for antidepressants (Model IV), SUBD for benzodiazepines (Model V)

Discussion

The study of secular trends in mental health is a matter of historical and current importance. Already in 1980, Srole and Fischer challenged claims of deteriorating mental health in successive generations, which had been postulated by the Mental Paradise Lost doctrine.[16] To date, however, major depressive disorder (MDD) has become the second leading cause of Years Lost to Disability worldwide.[5] The most important conclusion to be drawn from this study is that we found a substantial secular trend in the prevalence of MDD among late middle-aged adults, which is influenced by a dynamic equilibrium of more or less modifiable risk and protective factors.

Contrary to our expectations, we found an almost twofold increase in MDD prevalence in 2002 and 2012 as compared to 1992. The prevalence of MDD remained stable between 2002 and 2012. The increase in MDD rates was largely attributable to an increase in the prevalence of health problems in the two more recent cohorts, including chronic diseases, functional limitations, arthritis, COPD, pain and sleep problems. Moreover, if the prevalence of cardiovascular disease, smoking, loneliness and neuroticism had not decreased and mastery, labor market participation, network size and exchange of social support had not increased, the prevalence of MDD would have been 1.2 and 2.4 times higher in 2002 and 2012, respectively. Furthermore, we observed a 32% decline in SUBD prevalence in 2012 as compared to 2002, which was entirely associated with a decrease in risk and an increase in protective factors mainly from psychosocial domains of functioning.

The finding that MDD is more prevalent in successive generations has been extensively described.[6–11] However, other studies have found that the prevalence of MDD is stable.[12–14,17]

MDD in 2012 (vs. MDD in 1992)			SUBD in 2012 (vs. SUBD in 2002)		
OR_{Cohort}	OR_{Change}, %	95% CI	OR_{Cohort}	95% CI	OR_{Change}, %
1.80		**1.03,3.14**	**0.68**	0.48-0.96	
4.39	Ref	**2.05,9.37**	**0.68**	0.48-0.96	Ref
3.76	-19	**1.64,8.64**	1.25	0.83-1.88	+178
3.00	-41	**1.25,7.25**			
			1.26	0.84-1.90	+181

Moreover, a debate is ongoing whether increasing MDD rates constitute a 'true' increase or is due to methodological heterogeneity and recall artifacts.[15,20] Warshaw et. al. (1991) has refuted that recall artifacts explain secular trends in MDD prevalence.[60] Few scholars have examined secular trends in SUBD prevalence. Recently Wiberg et. al. (2013) has found that SUBD prevalence increased substantially among 75-year olds from 1976-1977 to 2005-2006.[18] This discrepant finding may be attributed to differences in age range, but this needs further study.

For a few known risk and protective factors of depression secular trends have been described in the literature to date, however, for the majority of factors this information was largely lacking. The finding that more recent cohorts were more exposed to chronic diseases, diabetes mellitus, arthritis, COPD, sleep problems and disability corresponds to other studies.[1,26,61] In western societies the overall prevalence of chronic diseases is increasing due to the aging of the population and the greater longevity of people with chronic conditions. Crimmins and Beltran-Sanchez (2011) reviewed literature on trends in mortality and morbidity in the United States and found that although mortality has declined, the prevalence of diseases has increased.[26] Also, mobility functioning has deteriorated and length of life with disease and mobility functioning loss has increased between 1998 and 2008. Literature is available that found the same deteriorating health trends for the situation in the Netherlands using different data.[62] Also a decrease in prevalence of CVD and smoking was found, which have been previously described.[2,25] Remarkable was the finding that neuroticism, a personality trait strongly associated with a genetic predisposition, declined in more recent cohorts. A possible explanation might be that neuroticism later in life is influenced more by non-genetic factors, such as occupation, however this issue needs further empirical study. The finding that

educational level, labor market participation, mastery and network size had increased in more recent cohorts has been supported by others and indicate that socioeconomic and psychosocial circumstances have improved for more recent generations.[30,63,64] The finding that an increased use of antidepressants in 2002 and 2012 as compared to 1992 had an additional explanatory effect on the secular trends found in MDD prevalence may be the consequence of improved recognition and treatment of MDD,[13,17,55] possibly since the introduction of selective serotonin reuptake inhibitors (SSRIs) around 1990. Antidepressants may be seen as a proxy for the (increased) recognition and detection of people with MDD. Sonnenberg and colleagues (2008) already found that the rise in the use of antidepressants between 1992 and 2002 was mainly attributable to a rise in the use of SSRIs.[55]

A major strength of this population-based epidemiological study is the rigorous design. LASA is primed to examine cohort differences in a reliable and valid manner by using identical measurements across cohorts, including a two-stage screening design to identify cases of SUBD and cases with a past-year diagnosis of MDD. The approach to include SUBD in the cohort comparison is, to our understanding, unique and important because evidence has been collected that SUBD is also a crucial determinant of public health and major risk factor for MDD.[19,65] Furthermore, essential information was gathered concerning secular trends in risk and protective factors for depression, which can be vital for future research. Some limitations need to be taken into account. First, the cross-sectional observational design does not allow causal conclusions and cannot distinguish well between cohort and period effects. It is unclear whether the more recent cohorts were especially prone to MDD (birth cohort factors) or that 2002 and 2012 were especially depressing times (period factors). Second, because the cooperation rates of the three cohorts ranged between 62% and 63%, this design holds the risk of selective non-response bias. However, the cooperation rates of the three cohorts are quite similar. Third, this study cannot answer the question whether an increased influx of new MDD cases, i.e. higher incidence, or an increased chronicity of prevalent MDD cases contributed to the higher prevalence found in recent cohorts. Future research should focus on longitudinal cohort differences with regard to the (first) onset, course and outcome of depression, including disability and mortality.

Nevertheless this study has important implications. Assuming that MDD rates 'truly' increase, despite improvement in psychiatric treatment, socioeconomic and psychosocial circumstances, we can expect a continued increase in burden of disease that will challenge the field of mental and public health. The finding that an increase in chronic diseases and functional limitations was associated with an increase in MDD in more recent generations of 55-64-year-olds is alarming, since the number of older people in

the population is growing and, simultaneously, those suffering from one or more chronic diseases and functional impairments. Moreover, in a previous study on the long-term prognosis of SUBD,[65] we found that community-dwelling older adults with SUBD were particularly at risk of developing MDD when chronic diseases, high BMI, or unhealthy lifestyles were present. Lessons must be learned from somatic medicine, as cardiovascular disease (CVD) has become less prevalent in recent decades through a lower exposure to CVD risk factors.[2] From a public health policy perspective, caregivers should pay attention to the presence of clinically relevant depressive symptoms in the growing group of people that is (or becomes) medically and physically compromised. This role may be suited to the general practitioner, but do also apply to the medical specialist in the hospital who treats patients with chronic diseases. Subsequently, for the purpose of indicated prevention of major depressive disorder, psychiatric counseling may be arranged. Additionally, physical activity has been associated with helping individuals maintain good physical and cognitive function throughout life and in older adults also with developing fewer chronic diseases,[66] which in turn may contribute to the prevention of depression in later life.

To conclude, our study showed a pessimistic prospect of increasing MDD rates, however SUBD rates showed a recent decline. Putative targets were identified for the purpose of preventive psychiatry and public health policies, which may help to reduce the worldwide disease burden of depression.

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Supplemental

eTable 1. The relationship between multiple risk and protective factors with major and subthreshold depression

	No depression (n = 2561)	SUBD (n = 211)	MDD (n = 94)	P Value
Female, No. (%)	1288 (50.3)	127 (60.5)	65 (69.1)	**<0.001**
Age, 55-64, mean (SD), y	60.1 (2.9)	60.4 (2.8)	59.6 (3.0)	0.065
Risk factors				
Lives in city, No. (%)	1463 (57.1)	138 (65.4)	66 (70.2)	**0.003**
# Chronic diseases, 0-7, median (IQR)	1.0 (1.0)	1.0 (2.0)	1.0 (2.0)	**<0.001**
≥1 Functional limitations, No. (%)	538 (21.0)	104 (49.5)	42 (45.2)	**<0.001**
Cardiovascular disease, No. (%)	346 (13.5)	46 (21.9)	22 (23.4)	**<0.001**
Diabetes, No. (%)	143 (5.6)	25 (11.8)	10 (10.6)	**<0.001**
Cancer, No. (%)	200 (7.8)	23 (10.9)	9 (9.6)	0.250
CVA, No. (%)	49 (1.9)	9 (4.3)	5 (5.3)	**0.009**
Arthritis, No. (%)	828 (32.4)	91 (43.3)	46 (48.9)	**<0.001**
COPD, No. (%)	207 (8.1)	37 (17.6)	19 (20.2)	**<0.001**
Body Mass Index, median (IQR)	26.6 (5.0)	27.2 (6.1)	26.6 (7.6)	0.151
Pain, 5-10, median (IQR)	5.0 (0.0)	6.0 (3.0)	5.0 (3.0)	**<0.001**
Sleep problems, 3-12, mean (SD)	5.5 (2.0)	7.1 (2.3)	7.4 (2.4)	**<0.001**
Alcohol consumption, No. (%)				**0.001**
None	254 (11.0)	43 (20.4)	17 (18.3)	
Moderate	1687 (73.0)	136 (64.5)	63 (67.7)	
Excessive	370 (16.0)	32 (15.2)	13 (14.0)	
Smoking, No. (%)	1001 (43.3)	113 (53.6)	53 (57.0)	**0.001**
Physical activity, min/day, median (IQR)	150.0 (140.7)	144.7 (145.1)	153.7 (114.3)	0.805
Neuroticism, 0-50, median (IQR)	3.0 (6.0)	9.0 (10.0)	14.0 (11.0)	**<0.001**
Loneliness, 0-11, median (IQR)	0.0 (2.0)	3.0 (5.0)	5.0 (5.0)	**<0.001**
Protective factors				
Religious, No. (%)	1341 (52.4)	94 (44.8)	48 (51.1)	0.105
Partner, No. (%)	2179 (85.1)	145 (69.0)	52 (55.3)	**<0.001**
Educational level, 5-18, mean (SD), y	10.6 (3.5)	9.8 (3.4)	10.3 (3.6	**0.007**
Labor market participation, No. (%)	1215 (47.7)	53 (25.7)	24 (25.5)	**<0.001**
Physical performance, 0-12, mean (SD)	9.0 (2.2)	7.8 (2.9)	8.0 (2.7)	**<0.001**
Cognitive functioning, 0-30, median (IQR)	28.0 (2.0)	28.0 (2.0)	28.0 (2.0)	**0.001**
Mastery, 5-25, mean (SD)	18.8 (3.0)	15.6 (3.6)	13.7 (3.8)	**<0.001**
Network size, 0-75, median (IQR)	15.0 (13.0)	11.9 (11.8)	13.0 (11.0)	**<0.001**
Exchange of social support, 0-36, mean (SD)				

eTable 1. Continued

	No depression (n = 2561)	SUBD (n = 211)	MDD (n = 94)	P Value
Instrumental support given	17.0 (6.8)	15.9 (7.1)	16.0 (7.4)	**0.037**
Instrumental support received	14.8 (6.2)	14.5 (6.8)	14.3 (6.9)	0.311
Emotional support given	23.4 (7.6)	22.6 (7.8)	22.2 (8.7)	0.126
Emotional support received	23.0 (7.4)	22.0 (8.2)	21.4 (8.7)	**0.044**
Antidepressants use, No. (%)	67 (2.9)	15 (7.1)	25 (26.9)	**<0.001**
Benzodiazepines use, No. (%)	113 (4.9)	28 (13.3)	31 (33.3)	**<0.001**
Cohort, No. (%)				**0.029**
Early (1992/1993)	856 (33.4)	68 (32.2)	20 (21.3)	
Middle (2002/2003)	843 (32.9)	84 (39.8)	38 (40.4)	
Recent (2012/2013)	862 (33.7)	59 (28.0)	36 (38.3)	

Chi-square values have been computed for categorical variables and t-values for interval variables. Independent-Samples Kruskal-Wallis Tests were used for non-parametric variables. #, number of; SD, standard deviation; IQR, interquartile range

Chapter 3

The tide has turned: Incidence of depression declined in community living young-old adults over one decade

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Abstract

Objective: Studying birth-cohort differences in depression incidence and their explanatory factors may provide insight into the etiology of depression and could help to optimize prevention strategies to reduce the worldwide burden of depression.

Method: Data were used from the Longitudinal Aging Study Amsterdam, a nationally representative study among community-dwelling older adults in the Netherlands. Cohort differences in depression incidence over a ten-year-period (score ≥ 16 on the Center for Epidemiological Depression scale) were tested using a cohort-sequential-longitudinal-design, comparing two identically measured cohorts of non-depressed 55-64-year-olds, born 10-years apart. Baseline measurements took place in 1992/93 (early cohort, n=794), and 2002/03 (recent cohort, n=771). As indicated by the dynamic equilibrium model of depression, potential explanatory factors were distinguished in risk and protective factors.

Results: The incidence rates for depression in the early and recent cohort were 1.91 (95% CI 1.59-2.27) and 1.60 (95% CI 1.31-1.94) per 100 persons-years, respectively. A 29% risk reduction in depression incidence was observed in the recent cohort (HR_{cohort}:0.71, 95% CI 0.54-0.92, p=0.011), as compared to the early cohort, even though average levels of risk factors such as chronic disease and functional limitations had increased. This reduction was primarily explained by increased levels of education, mastery, and labor market participation.

Conclusions: These findings suggest that favorable developments of protective factors have counterbalanced unfavorable effects of risk factors on the incidence of depression, resulting in a net reduction of depression incidence among young-old adults. However, maintaining a good physical health must be a priority to further decrease depression rates.

Introduction

It needs no introduction that depression is a major contributor to the global burden of disease at all ages.[1] Although there has been an increasing awareness in the recent decades of the need to better recognize and treat depression,[2] a majority of studies have observed an increase in depression rates among recent generations.[3] These findings have been largely based on prevalence studies,[4–6] while only very few have been able to investigate cohort differences in the incidence of depression.[7] Whereas prevalence rates provide information about the population burden of depression, they are the net-result of the combination of the incidence and the course of depression. For studying putative changes in the occurrence of new episodes of depression and the factors that are responsible for these trends, incidence rates are more accurate. Information on trends in incidence rates and their underlying mechanisms is essential for the design of prevention strategies to help to reduce the worldwide burden of depression.

Reasons for the lack of knowledge on cohort differences in the incidence of depression may be that the required nationwide prospective studies are scarce, expensive and time-consuming. Moreover, available studies provided evidence for both increasing and decreasing trends in incidence of depression, implying that the incidence fluctuates with time and place, and that studies should be repeated in different contexts. The Lundby study in Sweden has found a twofold increase in the incidence rate of depression when a 10-year period, 1947-1957, was compared with a subsequent 15-year period, 1957-1972.[8] However, a slight decrease in the incidence rate within the Lundby study had been observed in the period 1972-1997, as compared to the period 1947-1972.[9] The Sterling County Study in Canada has demonstrated a stable annual incidence rate of depression for the period 1952-1992.[10] A study on data collected from general practitioners (GPs) in the United Kingdom from 1996 to 2006 has demonstrated a decrease in the incidence of depression diagnoses, but an increase in the registration of depressive symptoms.[11] Most of these studies lacked the ability to identify explanatory factors for the trends found in depression incidence. Studying explanatory factors may reveal underlying mechanisms of trends in depression incidence, which can subsequently be addressed in preventive policy and medicine.

A useful model to understand the etiology and onset of depression is the dynamic equilibrium model of risk and protective factors, in which the balance of risk factors relative to protective factors determines the observed changes in incidence.[12] In a large meta-analysis on risk factors of incident depression among community-dwelling older adults (aged ≥ 50 years), Cole (2003) identified new medical illness, poor health status, prior depression, poor self-perceived-health, bereavement, sleep disturbance, disability

and female sex as the most important risk factors.[13] These findings suggest that health-related problems may be a central realm of risk of incident depression among middle-aged and older adults. In a previous study on cohort differences in the prevalence of depression, we confirmed that an increase in health problems was associated with an increase in depression prevalence in more recent cohorts of 55-64-year-olds in comparison with previous cohorts of age-peers.[5] Simultaneously, we found that average increases in protective factors, such as educational level, labor market participation, and sense of mastery, prevented the depression prevalence rates from having increased even further. These findings emphasize the importance of incorporating protective factors in studies on the incidence of depression.[5] From these findings, it may be assumed that the shift in depression prevalence among 55-64-year-olds is the net result of two broad underlying trends in recent generations, with opposing effects on depression: the shift towards increased levels of physical health problems (increased risk) on the one hand, and an improvement in overall socio-economic resources, such as education, access to work, and mastery (increased protection) on the other. Whether these trends in risk and protective factors of depression prevalence also explain cohort differences in depression incidence has not been studied yet.

The Longitudinal Aging Study Amsterdam (LASA) allows the identification and explanation of birth-cohort differences in the incidence of depression by using a long-term (ten years) follow-up in two identically-measured nationally-representative samples of 55-64-year-olds, who were non-depressed at baseline.[14,15] From a clinical point of view, 55-64-year-olds are a suitable target for prevention purposes of late-life depression. Moreover, this age group is of interest because they are young enough to have experienced changes in psychosocial and socioeconomic circumstances, and old enough to have experienced changes in health status, such as physical illness and functional limitations.[5]

The aim of the present study is to investigate and explain cohort differences in the incidence of depression. Based on our previous finding of an increase of depression prevalence,[5] we expected to find a higher incidence of depression in the recent cohort compared to the early cohort and that this increase in incidence rate could be explained by higher average levels of health-related risk factors in the recent cohort, as compared to the earlier cohort.

Methods

Study sample

Data were used from the Longitudinal Aging Study Amsterdam (LASA), an ongoing prospective cohort-sequential study among older adults in the Netherlands. Sampling procedures have been described previously.[14,15] In short, in 1992/93 the first cohort (N=3,107, birth years 1908-1937) was recruited from the population registries of eleven municipalities in three geographic areas of the Netherlands including a random sample of 55-84-year old men and women, stratified by age and sex according to the expected five-year mortality. The cooperation rate (the number of completed interviews divided by the total number of eligible persons) of the first cohort was 62%, also for the 55-64-year-olds subsample (birth years: 1928-1937). Follow-ups were conducted in 1995/96 (N=2,545), 1998/99 (N=2,076), and 2001/02 (N=1,691). Exactly 10 years after the first cohort, a new cohort (N=1,002, birth years 1938-1947) was recruited in 2002/03 including a random sample of 55-64-year-olds selected from the same sampling frame and measured identically to the first cohort. The cooperation rate for the second cohort was 62%. In subsequent observational cycles, respondents from the second cohort were combined with those from the first cohort. Follow-ups were conducted in 2005/06 (N=1,257), 2008/09 (N=985), and 2011/12 (N=614). All interviews were conducted in the homes of the respondents by trained interviewers. Written informed consent was obtained from all respondents. The Ethical Review Board of the VU University Medical Center approved the study.

To test our hypothesis on cohort differences in the incidence of clinically relevant depression, information was used on these two cohorts, for which follow-up of ten years was available at the time of this study. From both cohorts, respondents with a strict age limit of 55-64-years at baseline were included. Four observation cycles were used for each cohort. At the fourth observational cycle (2001-02 and 2011-12, respectively) respondents were aged 65-74. Respondents were excluded when having clinically relevant depression at baseline or lacked at least one follow-up measurement. The final sample consisted of N=1,565 respondents and a total of 12695 person-year observations. Of these 1,565 respondents, 794 respondents were from the first cohort and 771 respondents from the second cohort.

Measures

Dependent variable

The Center for Epidemiological Studies Depression Scale (CES-D) was applied to identify respondents with clinically relevant depression at each observational cycle (cut-off score CES-D ≥ 16).[16] The psychometric properties of the CES-D were found to be good.[17] Respondents without clinically relevant depression (CES-D < 16) were indicated as having no depression.

Main independent variable
A dichotomous variable denoting birth-cohort was constructed, with values for belonging to the 'early cohort' with baseline measurement in 1992/93, and the 'recent cohort' with baseline measurement in 2002/03.

Explanatory independent variables
Based on two literature reviews on risk factors of incident depression among community-dwelling older adults aged 55 years or older,[13,18] putative risk and protective factors were included from biological, psychological and social domains of functioning. According to the literature and based on biological plausibility, factors were considered either as risk or protective factors.

The following risk factors were included. The *number of chronic diseases* was assessed by self-report on current diseases and included cardiovascular disease, diabetes mellitus, cancer, cerebrovascular accident, arthritis and chronic non-specific pulmonary-disease (range, 0-7).[19] *Functional limitations* were measured by self-report and dichotomized in 'none' versus 'one or more' limitations.[20] *Body mass index* was calculated as measured body weight (kg) divided by measured height (m^2). *Pain* was measured with the Nottingham Pain Profile scale (range, 5-10).[21] *Sleep problems* were measured with a four-item self-completion questionnaire (range, 3-12).[21] *Alcohol consumption* was measured by the number of alcohol units consumed per day (u/d) and categorized into: abstainer (0 u/d), moderate (men, 1-3 u/d; women, 1-2 u/d) and excessive (men, ≥4 u/d; women, ≥3 u/d).[22] *Smoking* was dichotomized into 'current smoker or stopped ≤ 15 years ago' versus 'never smoked or stopped > 15 years'.[23] *Physical activity* was measured by the LASA Physical Activity Questionnaire, from which the total time in minutes per day spent on physical activity was calculated.[24] *Neuroticism* was measured with a 25-items subscale from the 36-item Dutch Personality Questionnaire (range, 0-50).[25] *Loneliness* was assessed with the De Jong-Gierveld Loneliness Scale (range, 0-11).[26]

The following protective factors were included. *Religiousness* was dichotomized in having a religion or not. *Partner status* was dichotomized in having a partner in or outside the household versus having no partner. *Education* was based on the number of years of education followed (range, 5-18). *Labor market participation* was assessed by self-report of having a paid job for more than one hour per week. *Physical performance* was measured with three performance tests, including walking, chair stand, and balance (range, 0-12, with higher scores indicating better performance).[27] *Mastery* was measured with a translated and abbreviated version of the Pearlin Mastery Scale (range, 5-25).[28] *Personal network size* was based on the total number of network members the respondent had regular contact with (range, 0-75); and the *exchange of social support* (both instrumental

and emotional) was collected for nine network members whom the respondent had the most frequent contact with (range, 0-36).[29]

Use of *antidepressants* and *benzodiazepines* were assessed by directly recording the medication from drug containers in the home of the respondents.[30] All measurement instruments were either previously validated in comparable samples in the Netherlands or in LASA pilot studies.[31] Because the dataset contained minimal 5% and maximal 25% missing values in some risk and protective factors, Multiple Imputation (MI) was performed, including 25 imputations and 50 iterations.

Statistical analyses

Descriptive statistics were performed on complete-cases data of the two cohorts pooled. The early cohort's data were weighted according to the distribution of age and sex in the recent cohort. This was done to make sure that changes in the incidence of depression, risk and protective factors reflected cohort differences and was not due to distributional differences in age and sex. Chi-square, *t* tests, and Kruskal-Wallis tests were performed to examine cohort differences in risk and protective factors of depression.

Further analyses performed with Cox proportional hazards regression were not weighted since all models were standard adjusted for age and sex. A basic model was created to test the association between 'cohort' and 'depression', adjusted for age and sex, to estimate the presence and degree of a cohort difference in the incidence of clinically relevant depression. The recent cohort was compared to the early cohort (=reference). All risk and protective factors were separately investigated for their explanatory ability. Potential explanatory factors were manually entered one by one into the basic model and the % change in hazards ratio of 'cohort' (HR_{cohort}) was estimated (Table 2). The % change in (HR_{cohort}) was calculated with following formulas: (($HR_{basic\ model} - HR_{model\ x}$) / ($HR_{basic\ model}$)) x 100.[32]

Factors were considered to be potentially explanatory when the magnitude of the association of cohort with depression incidence (HR_{cohort}) was reduced after adding them to the Cox regression model: thus decrease in HR if HR>1 or increase in HR if HR<1. Explanatory factors were considered to be suppressors when the opposite was observed: the magnitude of the association (HR_{cohort}) became stronger after adding them to the regression model: thus decrease in HR if HR<1 or increase in HR if HR>1. It is important to take into account suppressors in an explanatory analysis like this, because they indicate how much stronger the association (HR_{cohort}) would have been if these suppressing factors had remained stable over time.

Finally, multivariable analyses were performed to estimate the total percentage that could be explained by adjusting the basic model subsequently for the overall influence of suppressors, the overall influence of explanatory risk factors and finally for the overall influence of explanatory protective factors (Table 3). Data-analyses were conducted with SPSS v22.

Results

Cohort difference in depression incidence

From the 794 non-depressed respondents in the early cohort at baseline, 122 (15.4%) developed clinically relevant depression at follow-up. From 771 non-depressed respondents in the recent cohort at baseline, 101 (13.1%) developed clinically relevant depression at follow-up. The total time at risk in the early cohort was 76785 months (6399 years), whereas the total time at risk in the recent cohort was 75559 months (6297 years). The incidence rates for the early and recent cohort were 1.91 (95% CI 1.59-2.27) and 1.60 (95% CI 1.31-1.94) per 100 persons-years, respectively. The risk of developing clinically relevant depression in the recent cohort, adjusted for sex and age, was 29% less as compared to the early cohort (HR: 0.71, 95% CI 0.54-0.92), which is illustrated in Figure 1.

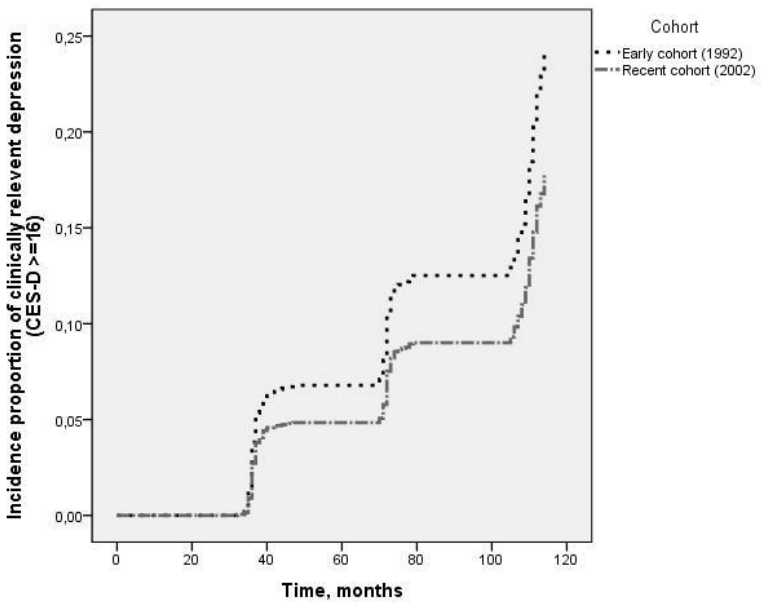

Figure 1. Decline in depression incidence among young-old adults between 2002-2012 versus 1992-2002

Cohort differences in risk and protective factors

Table 1 shows the cohort differences in risk and protective factors of depression between the early (1992/93) and recent (2002/03) cohort. The recent cohort had on average a higher level of education, more labor market participation, higher levels of mastery, of physical performance, of given instrumental and of given emotional support than the previous cohort. It also had lower average levels of neuroticism and smoking, but more chronic diseases, and functional limitations, a higher average body-mass-index, lower levels of physical activity and more excessive alcohol use, compared to the previous cohort. Finally, the use of antidepressants was higher in the recent cohort.

Explaining cohort difference in depression incidence

The contribution of each risk and protective factor to the difference in depression incidence between the cohorts is shown in Table 2. The differences in education (-9.9%), mastery (-7.0%), and neuroticism (-7.0%) contributed most to the difference in depression incidence. On the other hand, the high levels of functional limitations (+9.9%), chronic diseases (+5.6%), and excessive alcohol use (+4.2%) in the recent cohort suppressed the association of cohort with depression incidence. In other words, had these health-related factors remained constant, the incidence of depression would have decreased even further. Table 3 shows that the risk of developing depression in the recent cohort was 42% less (HR: 0.58, 95% CI: 0.43-0.79) as compared to the early cohort, after adjustment for all suppressors (model V).

The decrease in risk factors (neuroticism and smoking) explained 10% of the reduction in depression incidence (model VI), but the overall increase in protective factors (education, mastery, labor market participation, network size, instrumental and emotional support given, physical performance) explained the most part of the reduction in depression incidence (model VII). In total, 36% of the difference in depression incidence between the cohorts could be explained by all these risk and protective factors together.

Table 1. Baseline characteristics of non-depressed respondents by cohort

Variables	Early cohort 1992/93	Recent cohort 2002/03	p Value
No. observations, unweighted	794	771	
Female, no. (%)	406 (51.1)	385 (49.9)	0.64
Age, 55-64, mean (SD), years	60.1 (2.8)	59.9 (2.9)	0.084
No. observations, weighted	793	771	
Protective factors			
Education, mean (SD), years	9.6 (3.3)	10.6 (3.4)	**<0.001**
Labor market participation, no. (%), yes	251 (32.0)	358 (46.4)	**<0.001**
Mastery, mean (SD)	18.3 (3.1)	18.8 (3.0)	**0.003**
Religious, no. (%), yes	482 (60.7)	413 (53.6)	**0.004**
Partner, no. (%), yes	678 (85.4)	674 (87.4)	0.24
Network size, median (IQR)	14.0 (12.0)	14 (12.0)	0.68
Exchange of social support, mean (SD)			
Instrumental support given	16.1 (7.0)	17.4 (6.9)	**<0.001**
Instrumental support received	14.5 (6.4)	14.8 (6.3)	0.36
Emotional support given	21.6 (7.8)	24.2 (7.4)	**<0.001**
Emotional support received	23.1 (7.5)	22.6 (7.6)	0.24
Physical performance, mean (SD)	8.7 (2.3)	9.2 (2.2)	**<0.001**
Risk factors			
Neuroticism, median (IQR)	4.0 (6.0)	4.0 (6.0)	**0.009**
Loneliness, median (IQR)	0.0 (2.0)	1.0 (2.0)	0.80
Sleep problems, mean (SD)	5.4 (2.0)	5.5 (2.0)	0.66
Pain, median (IQR)	5.0 (0.0)	5.0 (1.0)	0.11
≥ 1 Chronic diseases, no. (%)	359 (45.3)	396 (51.4)	**0.016**
≥ 1 Functional limitations, no. (%)	117 (14.8)	164 (21.3)	**0.001**
Body-mass-index, median (IQR)	26.4 (4.3)	27.0 (5.1)	**0.003**
Physical activity, median (IQR), minutes/day	173.6 (158.7)	143.2 (137.5)	**<0.001**
Alcohol use			**<0.001**
Abstainer	101 (13.9)	48 (6.6)	
Moderate use	543 (74.7)	534 (73.2)	
Excessive use	83 (11.4)	148 (20.3)	
Smoking, no. (%)	366 (50.1)	314 (43.0)	**0.006**
Clinically relevant depression at follow-up, no. (%)	122 (15.4)	101 (13.1)	0.20
Psychotropic medication			
Antidepressant use, no. (%), yes	5 (0.7)	22 (3.0)	**0.001**
Benzodiazepine use, no. (%), yes	42 (5.7)	39 (5.3)	0.74

No. = number; SD = standard deviation; IQR = interquartile range. Bold = statistically significant at $p < 0.05$
X^2 values have been computed for categorical variables, t-values for interval variables, and independent-sample Kruskal-Wallis tests were conducted to determine non-parametric variables

Table 2. Factors associated with the decrease in the incidence of depression in the recent cohort

	Incidence of depression (CES-D≥16)			
	HR_{Cohort}	HR_{Change} %	95% CI	p Value
Recent cohort (versus early), unadjusted	0.70		0.54-0.92	0.010
Recent cohort (versus early), age and sex-adjusted	0.71	reference	0.54-0.92	0.011
Protective factors				
Education	0.78	-9.9%	0.59-1.02	0.069
Labor market participation	0.75	-5.6%	0.65-0.86	0.032
Mastery	0.76	-7.0%	0.58-0.99	0.049
Religious	0.71	0%	0.54-0.93	0.011
Partner	0.71	0%	0.54-0.93	0.013
Network size	0.72	-1.4%	0.67-0.88	0.054
Exchange of social support				
Instrumental support given	0.74	-4.2%	0.57-0.96	0.027
Instrumental support received	0.71	0%	0.62-0.81	0.011
Emotional support given	0.74	-4.2%	0.56-0.97	0.028
Emotional support received	0.71	0%	0.62-0.81	0.011
Physical performance	0.73	-2.8%	0.56-0.96	0.023
Risk factors				
Neuroticism	0.76	-7.0%	0.58-0.99	0.046
Loneliness	0.71	0%	0.62-0.81	0.012
Sleep problems	0.70*	+1.4%	0.53-0.93	0.015
Pain	0.69*	+2.8%	0.53-0.90	0.007
≥ 1 Chronic diseases	0.67*	+5.6%	0.51-0.88	0.004
≥ 1 Functional limitations	0.64*	+9.9%	0.49-0.84	0.001
Body-mass-index	0.69*	+2.8%	0.53-0.91	0.008
Physical activity	0.70*	+1.4%	0.53-0.91	0.009
Alcohol use	0.68*	+4.2%	0.52-0.90	0.007
Smoking	0.72	-1.4%	0.55-0.95	0.018
Psychotropic medication				
Antidepressant use	0.71	0%	0.54-0.93	0.013
Benzodiazepine use	0.71	0%	0.54-0.93	0.013

HR = Hazard Ratio; CES-D = Center for Epidemiological Scale Depression; * Suppressors

Table 3. Multivariate models explaining the decrease in depression incidence in the recent cohort

	Incidence of depression (CES-D≥16)			
	HR_{Cohort}	HR_{Change} %	95%-CI	p Value
Blockwise				
Basic Model (BM)	0.71	reference	0.54-0.92	0.01
Model II. BM + increase in protective factors	0.93	-31%	0.70-1.24	0.62
Model III. BM + decrease in risk factors	0.77	-9%	0.59-1.01	0.06
Model IV. BM + increase in risk factors (suppressors)	0.58	+18%	0.43-0.79	<0.001
Stepwise				
Model V. Model IV (suppressors)	0.58	reference	0.43-0.79	<0.001
Model VI. Model V + III (explanatory risk factors)	0.64	-10%	0.47-0.86	0.003
Model VII. Model VI + II (explanatory protective factors)	0.79	-36%	0.57-1.09	0.15

CES-D: Center for Epidemiological Studies Depression Scale. Variables included in models:
Basic Model (BM) = cohort, adjusted for age and sex; Model II = BM + education, mastery, labor market participation, network size, instrumental and emotional support given, physical performance; Model III = BM + neuroticism and smoking; Model IV = BM + functional limitations, chronic diseases, alcohol use, pain, body mass-index, sleep problems, physical activity

Discussion

This study found a substantial cohort difference in the ten-year incidence of clinically relevant depression between two cohorts of 55-64-year-olds: those from the recent cohort developed clinically relevant depression less often than the earlier cohort. The difference amounted to a 29% lower incidence risk observed in the recent cohort. The difference was primarily related to favorable developments in protective and resilience related factors, including an increase in levels of education, mastery and labor market participation. Had risk factors, such as chronic diseases and functional limitations, not increased in the recent cohort compared to the earlier cohort, the incidence difference would have been even larger. Although this finding indicates that chronic diseases and functional limitations are indeed important risk factors for developing depression, their relatively high levels in the recent cohort had not resulted in an increase in depression incidence between the cohorts, thereby falsifying our initial hypothesis. In terms of the dynamic equilibrium theory of depression, we conclude that the favorable developments in protective factors has outweighed the concurrent negative effects of developments in risk factors of depression.

Our study adds new knowledge to previous work, because published epidemiological studies on trends in depression rates have mainly focused on cohort differences in the prevalence,[7] rather than incidence of depression. The majority of these prevalence studies have reported an increase in depression rates.[3] The observed incidence rates of depression in this study from the early (1.9 per 100 person-years) and recent cohort (1.6 per 100 person-years) are both of comparable magnitude as those in other studies.[7] However, increasing,[8] decreasing,[11,33] and stable trends in depression incidence have all been reported.[10] Comparing these studies is extremely difficult, because different samples and study designs have been used, and findings refer to different period and social contexts. When comparing our previous trend study in depression prevalence (higher rates),[5] with the current trend study in depression incidence (lower rates), it may be suggested that a higher prevalence is due to an increasing chronicity of depression in more recent cohorts, which has also been suggested by Eaton and colleagues using data from the Baltimore Epidemiologic Catchment Area Study.[33]

To our knowledge no previous study has addressed explanatory factors of cohort differences in a systematic way by using the dynamic equilibrium theory of depression. Our study identified a combination of risk and protective factors that together explained approximately one third of the difference in depression incidence. The protective role of education and sense of mastery in preventing the onset of depression is well known,[12] however, to our knowledge the protective role of labor market participation has not yet been reported. It may be that young-old adults from the recent cohort have profited from changing societal attitudes toward being open about mental illness and seeking help,

which may be related to higher average educational levels, increases in participation in gainful employment and higher experienced levels of mastery.

The most important strengths of the present study are the cohort-sequential study design in which identical methods were used to recruit and measure random samples of the 55-64-year old population in the Netherlands. We had large enough samples to be able to select those without depression at baseline, following them up for longer periods (ten years) testing for differences in the incidence of depression. The relatively rich collection of risk and protective factors has enabled systematically testing the effects of putative risk and protective explanatory factors. Because both cohorts are identically measured, using long-term follow-ups with low dropout rates, our finding is not likely the result of an artifact. In addition, the study focused on a broad, but well-defined, definition of clinically relevant depression, because it has become clear that milder variants of depression also have a huge impact on the public health burden.[34] A number of limitations must be acknowledged. By using a three-yearly follow-up measurements, the incidence rate of depression may be underestimated since the occurrence of depression between follow-up measurements could have been missed. However, this is not likely to have affected the cohort comparison much, because each cohort had the same follow-up schedule. Secondly, solely baseline explanatory factors were included to facilitate the interpretation of cohort differences found. This may be a less sensitive method than studying time-varying factors, as risk and protective factors can change during ten years of follow-up. Finally, about two third of the decline in incidence could not be explained by factors included in this study, suggesting that other factors have been important also.

To conclude, this study has demonstrated that the depression incidence fluctuates, which is largely influenced by changing risk and protective factors of depression in the community. This also led to the identification of important targets for prevention strategies. For policy makers, the most important message is that the incidence of depression is far from a stable trait of a community, and that it can be influenced. As many of the important protective factors are essentially environmental and man-made factors, this shows that policies aiming to strengthen resilience can indeed have substantial effects on the incidence of a major mental illness, such as depression.

Future research should investigate whether the same trends can be found and explained in other age groups, and in other countries. Furthermore, also cohort differences in the natural course of depression have to be investigated, because the course together with the incidence of depression determines the prevalence, i.e. burden of disease. More detailed insight into time trends of depression will help the field to move forward in the global priority to reduce the disease burden of depression.[35]

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Chapter 4

Secular trends in excess mortality of late-life depression

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Abstract

Objective: Late-life depression is associated with premature mortality, however, little is known whether excess mortality rates of depression have changed over time. This study aims to identify and explain secular trends in excess mortality of major depressive disorder (MDD) and subthreshold depression (SUBD).

Method: Cohort-sequential-longitudinal study of 4,084 community-dwelling older adults in the Netherlands based on data from the Longitudinal Aging Study Amsterdam (LASA). Six measurement cycles were included from 1992/93 until 2008/09, each linked to the overall 5-year mortality, covering a 16-year time span. MDD and SUBD were identified using a two-stage screening procedure with the Center for Epidemiological Studies Depression Scale and the Diagnostic Interview Schedule. Age and sex were covariates. Education, health and lifestyle factors, and use of antidepressants were included as putative explanatory factors. Generalized Estimating Equations was used to investigate the association between the interaction 'Depression x Time' and 5-year mortality, and to find explanatory factors for the trend.

Results: A downward trend in excess mortality of MDD was found (OR=0.92, 95%-CI:0.85-0.99, *P*=.04), adjusted for age and sex, which could not be explained by education, health and lifestyle factors, nor antidepressants use. Sex differences in the trend were not found (*P*=.77). No trend in excess mortality of SUBD was found (OR=1.01, 95%-CI: 0.97-1.04, *P*=.65).

Conclusions: The results indicate a favorable development in excess mortality of community-dwelling older adults with MDD, while those with SUBD do not show a clear trend in excess mortality.

Introduction

The relationship between depression in later life and excess mortality has been studied extensively.[1,2] Although subthreshold depression (SUBD) and major depressive disorder (MDD) are both associated with premature mortality,[3,4] little is known whether excess mortality rates of depression have changed over time. A body of evidence support the hypothesis that premature mortality in late-life depression has been largely due to mortality from cardiovascular disease (CVD).[5–8] Since premature mortality from cardiovascular disease has decreased substantially in recent decades,[9,10] excess mortality of depression may also have declined in recent decades. However, this remains to be explored.

Previous research has revealed that the substantial decline in mortality rates from cardiovascular disease has been attributable to improved medical therapies and reductions in CVD risk factors, such as total cholesterol, systolic blood pressure and smoking.[9] Since a reciprocal relationship has been suggested between cardiovascular disease and late-life depression,[11] meaning that CVD is an important risk factor for depression and vice versa, it is important to explore if survival gains in CVD also have improved the prognosis of late-life depression, i.e. reduced excess mortality in late-life depression.

It has been debated whether sex differences play a role in excess mortality of depression.[12] While depressive disorders are more common among women,[13,14] higher mortality rates have been found among men.[12,14] Mechanisms that could explain these differences remain largely unclear. Moreover, a higher reduction in cardiovascular mortality has been observed among men,[9] which may have led to sex differences in the excess mortality trend of people with depressive disorder. Taken together, these findings implicate that it is important to address sex differences when investigating secular trends in excess mortality of depression.

The Longitudinal Aging Study Amsterdam (LASA) is suitable to examine secular trends in excess mortality of late-life depression by using identical measurements in comparable age groups over time. We hypothesize that there is a downward trend in excess mortality of late-life depression, in particular among men, which can be explained by a decrease in cardiovascular mortality. This study aims to: 1) investigate whether a secular trend in excess mortality of late-life depression exist, 2) if a secular trend is present, to investigate sex differences in the trend, and 3) to find explanatory factors for the trend in 65-84-year-olds over a period of sixteen years.

Methods

Study Design and Participants

Data were used from the Longitudinal Aging Study Amsterdam (LASA), an ongoing prospective population-based study that started in 1992/93 and focuses on changes in physical, emotional, cognitive and social functioning of respondents initially aged 55-85 years in the Netherlands.[15,16] Respondents were randomly selected from the registers of 11 municipalities in three different socio-demographic regions in the Netherlands, obtaining a representative sample of the Dutch older adult population. In 1992/93, 3,107 respondents took part in the LASA baseline interview (T1), with a cooperation rate of 62%. Follow-up measurements took place every three years and were conducted in 1995/96 (T2, N=2,545), 1998/99 (T3, N=2,076), 2001/02 (T4, N=1,691), 2005/06 (T5, N=1,257) and 2008/09 (T6, N=835). In 2002/03, a new sample was recruited following the same sampling frame as the first cohort with a cooperation rate of 62% (aged 55-64; N=1,002). Follow-ups were carried out in 2005/06 (N=908) and 2008/09 (N=833). Informed consent was obtained before the study, in accordance with legal requirements in the Netherlands.

For the present study, at each measurement cycle respondents aged between 65-84 years were included to make the samples comparable in age over time, i.e. over the six measurement cycles. Those without valid data on the dependent variable 'mortality' (N=32, 0.4% of total sample) were excluded. The pooled data-set comprised 9,093 observations over six measurement points from 4,084 respondents. The association between depression at each measurement cycle and overall mortality within 5-years (5-year mortality) was studied for each measurement cycle, covering a 16-year time span of mortality. Figure 1 provides an overview of the cohort-sequential longitudinal design.

Measurements

Mortality

Death certificates were traced through the registries of the municipalities in which the respondents were registered. All deaths that occurred between the baseline interview and July 1, 2015, were recorded. The vital status ascertainment was 99.6% complete. For this study, overall mortality within 5 years from each measurement point was determined.

Depression

At each measurement cycle, a two-stage-screening design was used to identify depression status. First, the Center for Epidemiological Studies Depression Scale (CES-D) was applied to identify respondents with clinically relevant depression (cut-off score CES-D ≥ 16).[17] The

psychometric properties of the CES-D were found to be good.[18] Second, for respondents who screened positive in the first stage (CES-D ≥ 16), a structured diagnostic interview was performed within 2-8 weeks using the Diagnostic Interview Schedule (DIS).[19] The DIS has been designed for epidemiological research to diagnose major depressive disorder in a reliable and valid manner according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-criteria).[19] Respondents without clinically relevant depression (CES-D < 16) were considered as having no depression. Respondents with clinically relevant depression (CES-D ≥ 16) but without a past-year diagnosis of major depressive disorder (MDD) according to the DIS were considered as having subthreshold depression (SUBD). Respondents with clinically relevant depression (CES-D ≥ 16) and also a past-year diagnosis of MDD were considered as having MDD.

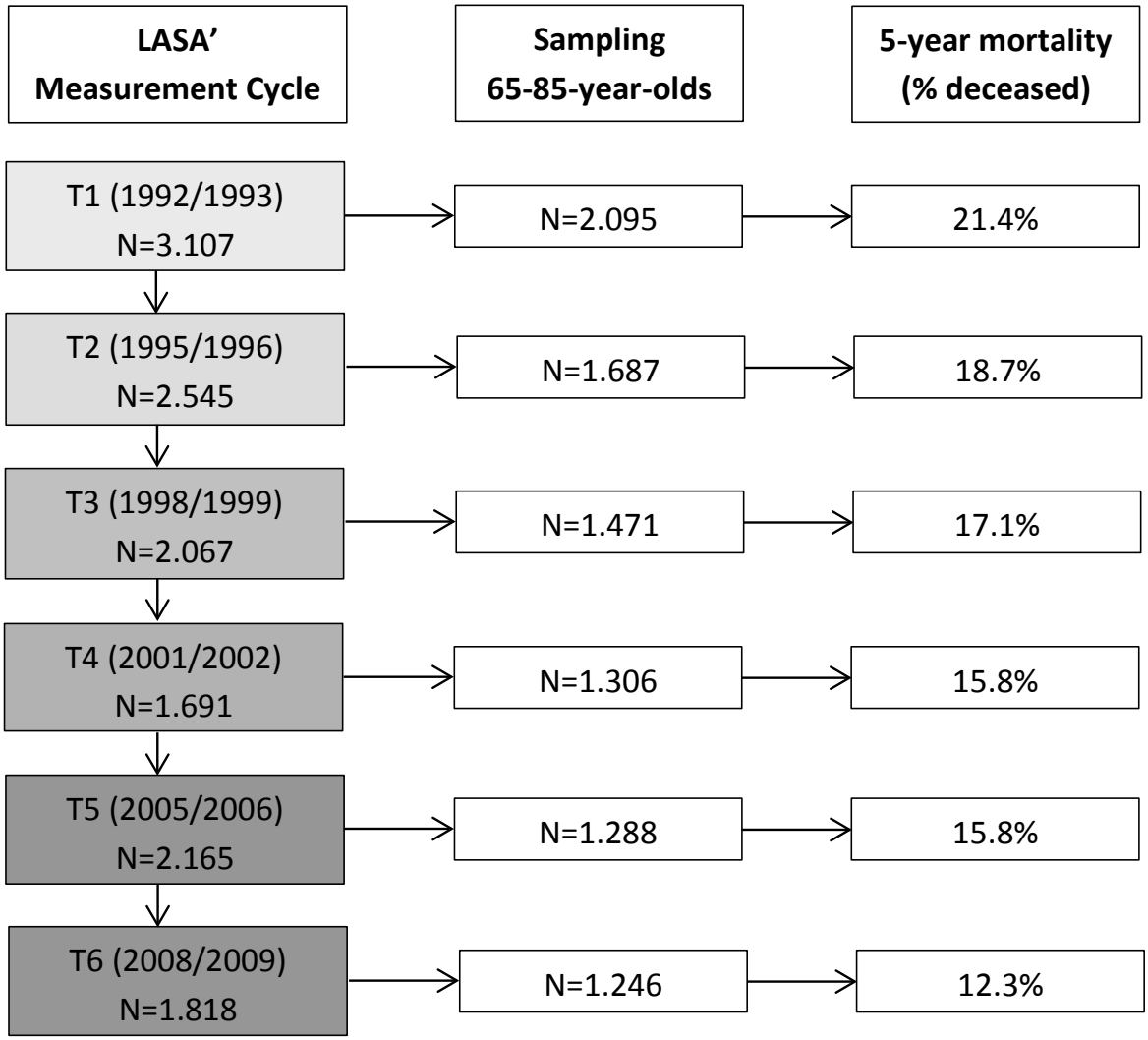

Figure 1. Overview of the cohort-sequential design in LASA used to identify secular trends in excess mortality of late-life depression

Covariates

Information on age and sex was derived from the population registries. To investigate to what extent 5-year mortality changed between 1992/93 and 2008/09, the variable time was created representing the study years (range 0-16 years).

Explanatory factors

Education in years (range 5-18) indicates the number of years a respondent received education. General cognitive functioning was measured with the Mini Mental State Examination (MMSE) (range 0-30; higher score indicates better functioning).[20] The presence of cardiovascular disease was self-reported, including at least one disease out of the three main categories: (a) cardiac disease, (b) peripheral arterial disease, or (c) cerebrovascular accident or stroke.[5] The presence of diabetes mellitus, chronic obstructive pulmonary disease (COPD) or asthma and cancer were also self-reported.[21] Functional limitations were measured as self-reported difficulty performing five common daily activities: walking up and down a fifteen step staircase without resting, getting dressed and undressed, sitting down and getting up from a chair, cutting own toenails and walking five minutes outdoors without resting.[22] The response categories were: (0) 'yes, without help'; (1) 'yes, with difficulty'; (2) 'only with help'; (3) 'no, I cannot'. The sum score ranged from 0-18 (higher score indicates worse functioning), which was dichotomized and coded as 0 = maximum 1 limitation, 1 = two or more limitations. Body Mass Index (BMI) was calculated as measured body weight (kg) divided by measured height (m2). Smoking was coded as 0 = never smoked or stopped > 15 years ago and 1 = current smoker or stopped ≤ 15 years ago).[23] Alcohol use was measured by the number of alcohol units consumed per day (u/d), which was categorized and coded as: 0 = moderate (men: 1-3 u/d, women: 1-2 u/d), 1 = abstainer (0 u/d) and 2 = excessive (men: ≥ 4 u/d, women: ≥3 u/d).[24] Use of antidepressants was assessed by directly recording the medication from drug containers in the home of the respondents.[25]

Missing data

Multiple Imputation (MI) was performed with 25 imputations and 50 iterations, because of more than 5% missing cases in the joint independent variables: in particular BMI (21.4%), alcohol use (19.2%), antidepressants use (18.8%), smoking (12.0%), depression status (12.0%) and cardiovascular disease (8.3%).

Statistical Analyses

Descriptive statistics were calculated for each measurement cycle (Table 1). As the mean age and percentage of women differs between the cycles, descriptive statistics were age and sex-weighted to T4 in order to ensure internal comparability between measurement cycles. This was done because the sample composition in T4, with respect to age and sex strata, most closely resembled that of the general Dutch older population at that time (2002).

For the analysis of mortality, Generalized Estimating Equations (GEE) was used.[26] A feature of GEE is that it takes into account the dependency of the repeated observations within persons by defining a correlation between errors. An unstructured correlation structure showed the best fit. The interpretation of the coefficient acquired in GEE is comparable to a regression coefficient in cross-sectional logistic regression. Time was included as a continuous variable in our models, which assumes a linear relationship between depression and mortality over time. Prior to the subsequent analyses, we tested whether this assumption was valid by investigating time as a categorical variable in GEE. According to the separate regression coefficients at each of the six measurement cycles, a linear relationship was largely confirmed.

To investigate whether a secular trend of excess mortality in late-life depression was present, interaction effects between time and depression status were tested (Table 2, model II), adjusted for age and sex. If an interaction term was statistically significant at $P < .10$, a secular trend was considered to be present. According to Aiken & West (1991), a P Value for trend of .10 was chosen so as not to overlook a potentially important interaction effect.[27] If a secular trend was present, sex differences were investigated by adding a three-way-interaction term to the basic model (Table 2, model III). If the three-way-interaction term was statistically significant at $P < .10$, subsequent analyses were stratified by sex. Finally, explanatory factors for the secular trend in excess mortality were identified by additionally adjusting the basic model for each putative explanatory factor (Table 3). The percentage change in odds ratio of the interaction variable 'Time x Depression' was evaluated. A minimal change of 10% in odds ratio was defined as a relevant change, in which case the variable was kept in the model.[28] Data-analyses were conducted with SPSS v22.

Results

Table 1 shows the study sample characteristics for each measurement cycle. The overall 5-year mortality in successive cohorts of 65-84-year-olds in the Netherlands has gradually decreased from 21.4% to 12.3% between 1992/93 and 2008/09. In contrast, there is an increase in the prevalence of health problems, including cardiovascular disease, diabetes mellitus, cancer and functional limitations. The level of education, general cognitive functioning and use of antidepressants has increased in successive cohorts and the prevalence of smoking has decreased. The prevalence of COPD does not show a clear trend. The prevalence of depression fluctuated over time and ranged between 1.3%-2.8% and 7.4%-11.7% for MDD and SUBD respectively.

The unadjusted 5-year mortality rate at each measurement cycle by depression status, retrieved from data on complete-cases, is as follows. Of the people without depression, the five-year mortality rate was 23.1% at T1, 19.7% at T2, 16.0% at T3, 13.3% at T4, 13.6% at T5 and 9.9% at T6. In those with SUBD, the five-year mortality rate was 31.5% at T1, 20.3% at T2, 19.4% at T3, 13.9% at T4, 17.7% at T5 and 11.5% at T6. In people with MDD, the 5-year mortality rate was 31.7% at T1, 24.3% at T2, 17.6% at T4, 6.9% at T5 and 7.1% at T6. Figure 2 illustrates the secular trend in excess mortality of late-life depression, adjusted for age and sex. The rate of non-response due to other reasons than mortality was on average 5% and was not different across the six measurement cycles, X^2 (5) = 1.98, p=.85.

In Table 2 results are shown from multivariable analyses between late-life depression and 5-year mortality. From the basic model (Model II) it becomes clear that the interaction term 'Time x MDD' is associated with 5-year mortality at P < .10, showing a downward trend of excess mortality in major depressive disorder (OR=0.92, P=.04). The odds ratio (0.92) does indicate a statistically significant reduction in mortality risk over 16 years among persons that were exposed to major depressive disorder (MDD) compared to those who were not exposed to MDD. This is further clarified by doing stratified analyses according to depression status thereby calculating the odds ratio on mortality from MDD for two separate time points, for example, at 3 years the odds ratio is 1.75, whereas the odds ratio at 9 years is 1.05. The interaction term 'Time x SUBD' is not associated with 5-year mortality (P=.68), meaning no secular trend was found in excess mortality of SUBD. Because the three-way interaction by sex 'Time x MDD x Sex' (Model III) is not associated with 5-year mortality at P < .10 (P=.75), the downward trend in excess mortality of MDD is not different between both sexes. Consequently, subsequent analyses were not stratified by sex.

Finally, all independent variables were explored for their ability to explain the secular trend in excess mortality of major depressive disorder (Table 3). Because none of the variables included in this study solely caused ≥ 10% change in odds ratio, the downward trend in excess mortality of MDD could not be explained by one of these factors. After adjustment for all factors together, the downward trend in excess mortality of MDD became somewhat stronger (10%, P=.03). Sensitivity analyses, in which depression status was dichotomized (SUBD and no depression were grouped as one category versus MDD), confirmed the absence of sex differences in the excess mortality trend of MDD (P=.76) and neither yielded explanatory factors for the downward trend in MDD.

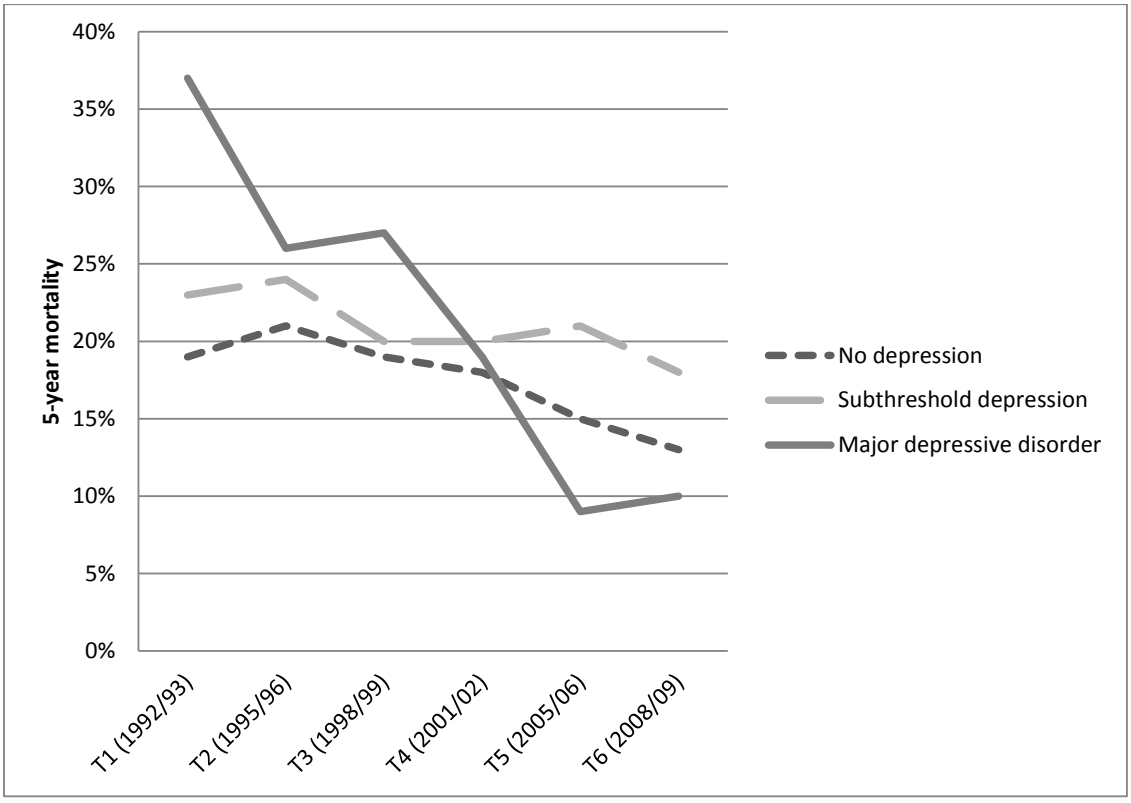

Figure 2. Downward trend in excess mortality of major depressive disorder among 65-84-year-olds, adjusted for age and sex

Table 1. Characteristics of respondents according to each measurement cycle, aged 65-84-years, Longitudinal Aging Study Amsterdam

	T1, 1992/93	T2, 1995/96
N observations, **unweighted**	2095	1687
Women (%)	51.2	53.1
Age, mean (SD), years	75.4 (5.8)	74.8 (5.8)
N observations, **weighted**[1]	2107	1668
Demographic variables		
Education, years, mean (SD)	8.4 (3.2)	8.7 (3.2)
Mortality, 5 year (%)	21.4	18.7
Health factors		
Depression (%)		
No depression	87.9	87.8
Subthreshold depression	9.6	9.8
Major depressive disorder	2.4	2.4
General cognitive functioning (MMSE), mean (SD)	26.6 (3.2)	26.8 (3.1)
Cardiovascular disease (%)	31.3	33.5
Diabetes mellitus (%)	9.3	8.3
Chronic Obstructive Pulmonary Disease (%)	13.1	14.9
Cancer (%)	11.0	12.5
≥ 2 functional limitations (%)	32.8	34.9
Lifestyle factors		
Alcohol use (%)		
Normal	70.6	68.2
Abstainer	26.2	25.7
Excessive	3.2	6.2
Smoking (%)	42.8	40.6
Body Mass Index, mean (SD),	27.0 (4.2)	27.0 (4.3)
Treatment factor		
Antidepressants use (%)	2.3	2.8

[1]Means and percentages are weighted to the age and sex distribution in T4

	T3, 1998/99	T4, 2001/02	T5, 2005/06	T6, 2008/09	*P* for trend
	1471	1306	1288	1246	
	55.7	56.9	56.4	55.7	0.883
	74.4 (5.8)	74.0 (5.5)	73.8 (5.7)	74.0 (5.7)	0.800
	1520	1306	1241	1184	
	8.9 (3.1)	9.2 (3.2)	9.5 (3.3)	9.9 (3.4)	<0.001
	17.1	15.8	15.8	12.3	<0.001
					0.065
	85.6	91.0	86.2	90.6	
	11.7	7.4	11.2	8.1	
	2.8	1.6	2.6	1.3	
	27.1 (2.9)	27.3 (2.9)	27.4 (2.6)	27.6 (2.5)	<0.001
	35.6	37.1	37.1	37.9	<0.001
	9.0	10.2	13.3	15.4	<0.001
	15.7	13.8	13.7	14.9	0.440
	14.8	15.3	16.3	16.3	<0.001
	37.9	41.0	42.9	36.9	<0.001
					<0.001
	77.8	77.2	76.6	75.1	
	18.9	19.5	18.5	20.0	
	3.2	3.3	4.8	4.9	
	33.6	33.6	33.3	31.4	<0.001
	27.5 (4.3)	27.5 (4.2)	27.6 (4.3)	27.5 (4.4)	<0.001
	4.1	5.5	4.7	4.6	<0.001

Table 2. Association between late-life depression and 5-year mortality over time and sex differences using generalized estimating equations (GEE)

	Model I		
	OR	95%-CI	*P* value
Time, one year (range: 0-16)	0.98	0.96-0.99	<0.001
Women (ref: men)	0.50	0.44-057	<0.001
Age	1.15	1.14-1.17	<0.001
Depression (ref: no depression)			
Major depression (MDD)	1.42	0.98-2.05	0.061
Subthreshold depression (SUBD)	1.23	1.02-1.47	0.027
Time x MDD			
Time x SUBD			
Time x Sex			
Time x Sex x MDD			

Note: N = 9,093 observations from respondents aged 65-84-years. Source: Longitudinal Aging Study Amsterdam between 1992/93 and 2008/09; OR = odds ratio

Table 3. Finding factors that explain the downward trend in excess mortality of MDD

	5-year mortality		
	OR $^{(\text{Time x MDD})}$	*P* value	% change in OR
Time x MDD (basic model)	0.92	0.040	Reference
Additionally adjusted for demographics			
Education	0.92	0.042	1
Additionally adjusted for health factors			
Cardiovascular disease	0.92	0.042	0
Diabetes mellitus	0.92	0.031	-2
Chronic Obstructive Pulmonary Disease	0.92	0.035	-2
Cancer	0.92	0.037	-1
General cognitive functioning	0.92	0.040	-2
≥ 2 functional limitations	0.92	0.047	2
Additionally adjusted for lifestyle factors			
Alcohol use	0.92	0.047	+2
Smoking	0.91	0.034	-4
Body Mass Index	0.92	0.038	-1
Additionally adjusted for treatment factor			
Antidepressants use	0.92	0.036	-2
Additionally adjusted for all factors	0.91	0.029	-10

Basic model is adjusted for age and sex; Each putative explanatory factor is separately entered to the basic model, in which the % change in OR is evaluated; ≥ 10% is defined as a relevant change; OR = odds ratio

Model II (basic model)			Model III (3-way interaction)		
OR	95%-CI	*P* value	OR	95%-CI	*P* value
0.98	0.96-0.99	<0.001	0.97	0.95-0.98	<0.001
0.50	0.44-0.59	<0.001	0.44	0.36-0.54	<0.001
1.15	1.14-1.17	<0.001	1.15	1.14-1.17	<0.001
2.25	1.38-3.67	0.001	2.32	1.42-3.80	0.001
1.17	0.90-1.52	0.25	1.19	0.91-1.55	0.20
0.92	0.85-0.99	0.04	0.90	0.79-1.02	0.11
1.01	0.97-1.04	0.65	1.01	0.96-1.06	0.70
			1.02	1.00-1.04	0.07
			1.02	0.90-1.16	0.75

Discussion

The main aim of this study was to examine whether a secular trend exist in excess mortality of late-life depression in the general community. The most important conclusion to be drawn from our study is that a downward trend in excess mortality was found for major depressive disorder (MDD), but not for subthreshold depression (SUBD) among 65-84-year-olds. In addition, no sex differences were found for the excess mortality trend of MDD. The 5-year mortality risk of 65-84-year-olds with MDD, compared to those without depression, was reduced over a period of sixteen years (OR=0.92). To indicate the difference, the 5-year mortality rate of older adults with MDD in 1992/93 and 2008/09 was 37% and 10%, respectively. However, we did not identify specific factors that explained the downward trend in excess mortality of MDD.

The link between depression and mortality is complicated because most people with depression do not die of their condition, but rather die of cardiovascular disease, other diseases, suicide, and other causes.[29] We hypothesized that a reduction in cardiovascular mortality may have contributed to a decline in mortality from late-life depression, in particular among men. Although our study found that the prevalence of CVD had increased, which corresponds to the observation that CVD has become less lethal in successive generations of 65-84-year-olds,[9,10] CVD did not explain the downward trend in excess mortality of MDD. None of the other variables included, such as education, health and lifestyle factors, nor use of antidepressants were found to be explanatory, which may collectively point to the influence of other factors yet unknown.

One explanation of the downward trend in excess mortality of MDD might be that recognition and treatment of MDD in later life has improved in recent decades.[30,31] The finding that use of antidepressants had increased in more recent generations is in accordance with current literature.[25] Although the decline in excess mortality of MDD could not be explained by the use of antidepressants, it has been found that an antidepressant prescription is a poor proxy for the adequacy of depression treatment.[32] The increase in the use of antidepressants has been associated with a decrease in suicide rates in the US.[33,34] However, it is not known whether this finding is generalizable to the Netherlands, and regardless, only a small proportion of excess mortality in MDD can be explained by suicides.[2,5] In a randomized control trial, Gallo and colleagues (2013) found that patients with MDD in practices provided with additional resources to intensively manage depression had a mortality risk 24% lower than that observed in usual care and similar to older adults without depression.[35] Nowadays much more attention is paid to the somatic screening (i.e. metabolic) and optimizing somatic treatments of psychiatric patients, particularly in old age. Once a patient receives specialist mental health care,

referral to a somatic specialist can easily be arranged when needed. This might not be true for the condition subthreshold depression (SUBD), where people have clinically relevant depressive symptoms but not fulfill diagnostic criteria for MDD.[36] It is plausible to assume that people with SUBD do not receive as much attention from medical care as people with MDD, which could be an explanation for the finding in this study that no secular trend was found in excess mortality of SUBD. However, this issue deserves further empirical study.

To date, little research has been available that report on trends in excess mortality of late-life depression. Lumme et. al. (2016) has recently studied trends in excess mortality among hospitalized patients with (severe) mood disorders in 1996-2010 in Finland.[37] The study reported a decrease of mortality in the period between 1996 and 2010, which was partly attributable to a reduction in alcohol-related mortality. From the Stirling County Study, Murphy et. al. (2010) has not found secular trends in excess mortality of depression among community-dwelling adults aged 18 years or older between 1952 and 1970.[38] However, both studies are difficult to compare with our study, because of methodological differences regarding the setting, age-range and period in which these studies were conducted. In a systematic review of excess mortality among (broadly defined) mental disorders, Walker et. al. (2015) has found that when studies were published more recently higher excess mortality rates were reported.[29] This led the authors to conclude that a mortality gap exists between people with mental disorders and the general population. Subsequently, Walker et. al. has suggested that people with mental disorders do not experience the increased life expectancy of the general population.[29] Our finding is contradictory, indicating that such 'mortality gap' might have closed for major depressive disorder in later life. However, more time trend studies conducted in different countries are needed to replicate these findings.

The strength of this study is the cohort-sequential longitudinal design, analyzed by Generalized Estimating Equations (GEE), which allowed the identification of a secular trend in a reliable and valid manner. Second, the approach to include SUBD in the analyses is important, because SUBD is an important determinant of public health,[36] and a major risk factor for MDD.[39] There are several limitations that need to be addressed. Because this is one of the first studies investigating trends in excess mortality of late-life depression, results should be interpreted with caution. The results do not imply a similar trend for other countries in the same geographical region. The number of cases with MDD, particularly at the last two measurement cycles, was small and a minority of those cases died within 5 years. However, since GEE takes into account mortality at all measurement cycles, the decrease in mortality associated with MDD is not likely an artifact of low rates. The P value (.04) and narrow confidence interval obtained with GEE

does indicate that unless limited power this finding is robust. Since the initial cooperation rate of LASA respondents has been 62%, the prevalence of depression at baseline may be underestimated, because depressed persons may be less likely to cooperate with such studies. On the other hand, the cooperation rate of LASA respondents at follow-up has been very good with an average non-response of 5%, which was not associated with having depression. Another limitation is that our study lacked information on the formal diagnosis of dementia, which may be an important confounder in the relationship between MDD and premature mortality. Finally, the study lacked information on specific causes of death, such as cardiac death or suicide, having this information could improve the specificity of the findings.

Nonetheless, the finding of a favorable trend in excess mortality of MDD is important for public health and clinicians. From a public-health perspective, it is first needed to better understand what is driving these secular trends in excess mortality among 65-84-year olds, before public health interventions can be initiated. Moreover, our findings have to be replicated in other studies, in other countries, which make use of more or less similar study designs and samples. Both policy makers and caregivers might appreciate that excess mortality of MDD in later life has changed in recent decades, as it may suggest that both prevention strategies and improved treatments of MDD provide a return on the investment in recent decades. However, attention should also be paid to the early recognition and treatment of SUBD, since no secular trend was found in excess mortality of SUBD.

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Chapter 5

The long-term outcome of subthreshold depression in later life

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Abstract

Objective: Subthreshold depression (SUBD) in later life is common and important as prodromal state and prominent risk factor in the development of major depressive disorder (MDD). Indicated prevention can reduce the incidence of MDD among people with SUBD substantially, but needs to be targeted to those that are truly at risk to develop MDD.

Method: N=341 eligible participants with SUBD were included from the first (1992/1993), second (1995/1996) and third cycle (1998/1999) from the Longitudinal Aging Study Amsterdam (LASA) by using a two-stage screening design. LASA is an ongoing prospective cohort study in the Netherlands among the older population (55-85 years). At baseline (1992/1993) N=3107 participants were interviewed and follow-up cycles were conducted every three years until 2008/2009, resulting in maximal 17-years of observational period. The proportion of people that developed MDD, remained SUBD, or recovered from SUBD was measured and Cox proportional regression analyses were performed to investigate twenty-nine putative predictors of MDD and recovery from SUBD.

Results: N=153 (44.9%) recovered from SUBD, N=138 (40.5%) remained chronically SUBD, and N=50 (14.7%) developed MDD (incidence rate: 15.1/1000 person-years). Women, high neuroticism, more chronic diseases, high body-mass-index, smoking and less social support predicted conversion to MDD. Men, low neuroticism and absence of pain predicted recovery from SUBD.

Conclusions: Although older people with SUBD are clearly at risk of developing MDD, the majority did not, even after a long and thorough follow-up. Given the risk factors that were uncovered, targeting and prevention of MDD in those at very high risk is feasible.

Introduction

It is widely believed that depressive symptoms exist on a continuum of severity that includes subthreshold depression (SUBD), a condition described as a clinically relevant level of depressive symptoms without meeting full diagnostic criteria for a major depressive disorder (MDD) according to the DSM or ICD.[1] Recent studies have shown that SUBD represents a large burden of disease,[2] both in individual patients and at the level of the community.[3,4] This burden is due to a combination of a high prevalence, prevalence rates estimated around 10% of all older adults,[5] and its effects on quality of life,[6] physical health,[7] disability,[8] mortality,[9] and health care utilization.[10]

Extensive literature is available documenting the effects of different strategies to prevent major depressive disorder.[11] These focus on (a) the whole population (universal prevention), (b) those at risk due to exposure to known risk factors for MDD (selective prevention) and (c) those at even higher risk of MDD due to their exhibiting prodromal signs and symptoms of depression (indicated prevention). Several studies among all age groups have demonstrated that indicated prevention of depression is feasible, effective and cost-effective.[12–14] Indicated prevention is delivered using low cost psychological interventions, such as cognitive-behavioral therapy, and may reduce the incidence of MDD at six months by 39%, yielding a number needed to treat (NNT) that was estimated at 10.[15] This compares favorably with preventative interventions elsewhere in medicine. For example, the NNT with any statin to prevent one case of cardiovascular disease over five years was estimated 33 and 37 respectively for men and women.[16]

Nonetheless, the availability and actual use of indicated prevention of MDD remains very limited in most countries. A recent study has shown that it requires much effort to reach eligible persons with depressive symptoms who are interested in accepting treatment.[17] Improving the selection of those older people, in whom preventative intervention may be feasible, may encourage the field to adopt prevention as a mainstream strategy.

SUBD may represent a prodromal state and important risk indicator for the later development of MDD,[5] a chronic mild depression or a transient, self-limiting mood state.[18,19] One implication of these findings is that the majority of those older patients eligible for indicated prevention would not develop MDD, thus wasting resources or even harming patients through iatrogenic effects. Psychological harm may arise from anticipated discomfort towards prevention programs or as a consequence of being labeled as 'sick' or 'at risk'.[20] Consequently it is crucial to distinguish between people who are truly at risk for MDD from those who are not. This requires detailed knowledge about the long-term prognosis of late-life SUBD and predictors of outcome, which are largely

lacking. The reported risks in previous studies were mainly based on follow-up periods of approximately one or two years.[5] The time frame at which MDD develops from SUBD in late life is not known, but this might well be longer than two years. In order to enhance indicated prevention strategies, studies with longer follow-up periods are needed to examine the long-term prognosis of late-life SUBD more precisely and examine predictors of its outcome.

A useful framework for understanding the etiology of depressive episodes in older community-dwelling adults has been the dynamic stress-vulnerability model (DSVM),[21] which implies that interplay between vulnerability and stress factors determines the risk of developing MDD, where pathogenic effects of stress are more pronounced when people are more vulnerable. According to this theory, variations in exposure to vulnerability and stress factors may account for differences in the long-term prognosis of SUBD.

In the present study, we investigate a wide range of vulnerability and stress related variables in a longitudinal design with up to 17-years of follow-up to identify both predictors of MDD and recovery in a population-based sample of older people with SUBD. We hypothesize that a substantial group of older adults with SUBD has short-lived and self-limiting symptoms, likely to be determined by concurrent psychosocial circumstances (stress related); and those more at risk of developing MDD are more likely to exhibit longstanding vulnerability for mood disorders.

Methods

Sampling

Data were used from the Longitudinal Aging Study Amsterdam (LASA), an ongoing prospective cohort study on determinants and consequences of changes in functioning in relation to ageing of community-dwelling older people in the Netherlands. Sampling, response and procedures are described in detail elsewhere.[22] In short, at the first LASA cycle in 1992 and 1993, a representative sample stratified by age, sex and degree of urbanization of N=3107 community-dwelling older people aged 55-85 years was interviewed. Since then, follow-up cycles have been conducted roughly every 3 years until 2008/2009, resulting in an observation period up to 17 years. Participants were interviewed at their homes, by well-trained interviewers. Written informed consent was obtained prior to study enrollment, in accordance with legal requirements in the Netherlands.

For the current study, data from the first (1992/1993), second (1995/1996) and third cycle (1998/1999) were used to compose a study sample of N=341 eligible participants with SUBD. Data for the predictor variables were taken from the corresponding incident cycle. Figure 1 shows the recruitment of participants with SUBD. Eligible for inclusion were participants aged 55-85 years identified as having SUBD on either of the first three LASA cycles and having at least one follow-up measurement after enrollment in this study. Participants were able to skip a follow-up interview and then rejoin the study. The proportion of the SUBD sample that was retained after 3-years of follow-up was 89.4%, after 6-years 66.9%, after 9-years 49.9%, after 12-years 34.4% and after 15-years 24.1%.

Measures

Prognosis of SUBD

The prognosis of late-life SUBD was based on the three outcome variables: 'subthreshold depression (SUBD)', 'major depressive disorder (MDD)' and 'recovery from SUBD'.

Subthreshold Depression (SUBD)

A two-stage-screening design was used to identify SUBD as follows. First, the Center for Epidemiologic Studies Depression Scale (CES-D) was applied to identify participants with clinically relevant depressive symptoms (cut-off score of CES-D ≥ 16).[23,24] The psychometric properties of the CES-D were found to be good.[25] Second, the Diagnostic Interview Schedule was scheduled for participants that screened positive in the first stage (CES-D ≥ 16) and took place 2-8 weeks after the CES-D interview. Participants with clinically relevant depressive symptomatology (CES-D ≥ 16) but without MDD diagnosis were indicated as having SUBD.

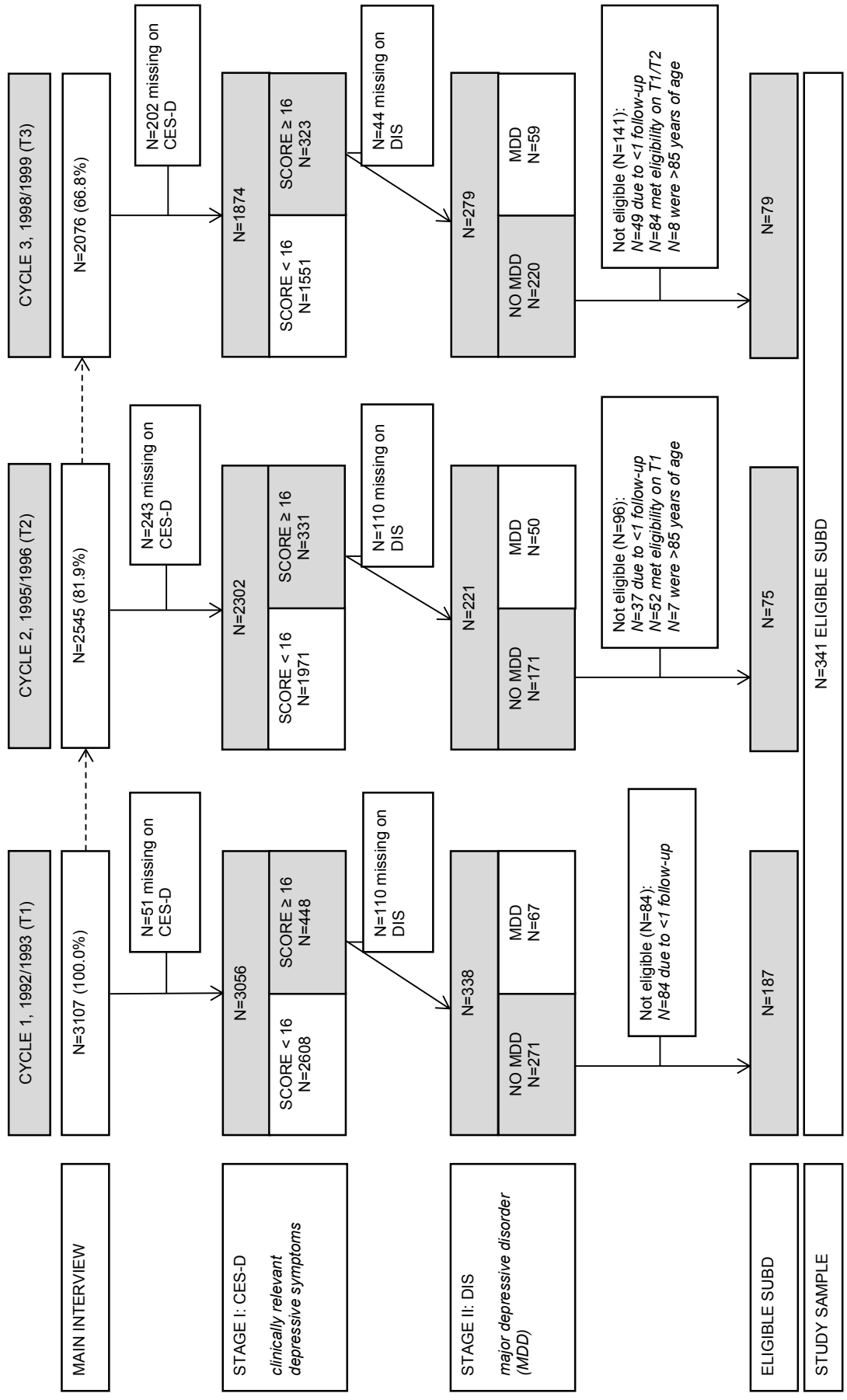

Figure 1. Sampling subthreshold depression (SUBD) by using a two-stage-screening design in LASA

Major Depressive Disorder (MDD)
The Diagnostic Interview Schedule (DIS), a structured interview designed for epidemiological research, was used at baseline and follow-up to diagnose dysthymic or major depressive disorder in a reliable and valid manner according to the Diagnostic and Statistical Manual of Mental Disorders - third edition (DSM-III).[26] Participants had to have a past-year diagnosis of MDD during follow-up. Timing of the MDD episode was calculated as the time point half way that year, thus follow-up time until the interview minus 6 months.

Recovery from SUBD
Recovery was defined as a combination of (I) a relevant decline in depressive symptomology (≥ 5 CES-D points) between two measurements during follow-up thereby crossing the CES-D cut-off score (CES-D = 16), and (II) remaining non-depressed (CES-D < 16) throughout the rest of the study. The difference of 5 CES-D points for a relevant decline fits in with the definition of a reliable change;[27] which takes into account the reliability, average score and standard deviation (SD) of the CES-D in LASA;[28] and with the principle of a medium effect size according to Cohen.[29] A similar definition and CES-D score of a relevant change was used in earlier studies.[18,28]

Predictors
Based on current literature,[30] twenty-nine putative predictors of MDD were selected from biological, psychological and social domains of functioning and subdivided into vulnerability and stress related variables according to the DSVM.

Among the vulnerability related variables; information on age and gender was derived from the population registries. Level of education was based on the number of years of education (range: 5-18 years). We opted for educational level as our socio-economic status indicator. Educational level has been the best indicator of lifetime socio-economic status across age and over time and is causally prior to other socio-economic indicators such as occupational status and income.[31] The degree of urbanization was assessed by using the classification of Statistics Netherlands, based on the postal codes of the Netherlands and was dichotomized into living in a city (>1000 no. addresses/km^2) or rural (<1000 no. addresses/km^2).[32] Both psychiatric and familial history of major depression were assessed with the DIS and used as a dichotomized variable (positive/negative). Neuroticism was measured by self-report with a subset of 25-items from the 36-item Dutch Personality Questionnaire (DPQ).[33] Scale scores range from 0-50 points with higher scores indicating a high neuroticism. Neuroticism is a major personality trait characterized by a reduced threshold to experience a broad range of negative emotions and the inability to cope with, including fear, sadness or depression and self-dissatisfaction. High scorers are socially

ill at ease and feel they cannot easily relate to other people and are more vulnerable to stress.[34] Mastery (locus of control) was measured by self-report with a translated and abbreviated Dutch version of the Pearlin Mastery Scale (PMS).[35] Scale scores range from 5-25 points with higher scores indicating a high mastery. The presence of an adverse early childhood event before the age of 6 years was assessed with the DIS and included 6 items: death of a parent; severe self-disease; physical abuse; (emotional) neglect; sexual abuse; and traumatic war experiences. A dichotomized variable was made indicating the presence or absence of any adverse life event during early childhood. General cognitive functioning was measured by the Mini Mental State Examination (MMSE).[36] Scores range from 0-30 points with higher scores indicating better cognitive functioning. The presence of a partner in or outside the household was assessed. The personal network size was defined as the total number of network members with whom the participant had important and regular contact (range: 0-75 members).[37]

Among the stress related variables; the number of chronic diseases in a person was included as an indicator of comorbid somatic disease since the number of people with particular medical diseases, such as diabetes mellitus, was too low to perform meaningful statistical analyses. The number of chronic diseases was based on self-report, concerning 7 major chronic diseases: chronic obstructive pulmonary disease, cardiac disease, stroke, peripheral arterial disease, diabetes mellitus, cancer, and rheumatoid arthritis or osteoarthritis.[38] The number of functional limitations were assessed with three questions about daily life functioning: to walk up and down a staircase of 15 steps without resting, to cut one's toenails, and to use one's own or public transportation. The number of limitations were summed and ranged from 0 to 3.[39] The severity level of depressive symptoms was measured with the CES-D. Anxiety symptoms were measured with a subscale from the Hospital Anxiety and Depression scale (HADS-A),[40] which consists of seven items resulting in a sum score ranging from 0 to 21 with higher scores indicating more anxiety symptoms. Sleep problems was measured with a three-item questionnaire;[41] scores were summed to a total (range: 3-12 points) with higher scores indicating more sleep problems. Reported pain was measured with a five-item questionnaire based on a subscale from the Nottingham Health Profile (NHP) pain scale;[41] with total scores ranging from 5 (no pain) to 10 (severe pain). Self-perceived health was assessed by self-report and included as a single question, with a 5-point scale which was dichotomized.[42] Use of alcohol was included as the standardized number of alcohol units consumed per day, corrected for gender, and classified as a categorical variable with three groups: abstainer (0 units p/d), moderate (men: 1-3 units p/d, women: 1-2 units p/d) and excessive consumption (men: ≥ 4 units p/d, women: ≥ 3 units p/d).[42] Smoking was dichotomized (yes/no). Body-Mass-Index (BMI) was calculated as measured weight (kg) divided by measured height in square meters (m^2). The number of recent negative life events, experienced between baseline

and follow-up, were adapted from the life-event inventory, developed by Tennant and Andrews,[43] consisting of: death or divorce of partner, death of a close relative, death of a grandchild, illness of partner, illness of relative, serious conflict with others, relocation, and being a victim of crime. The exchange of instrumental and emotional support was rated from 0 (never) to 4 (often).[44] Loneliness was assessed with the 11-item Loneliness scale (de Jong-Gierveld & Kamphuis 1985) with scores ranging from 0-11 points with higher scores indicating a higher level of loneliness. All scales were either previously validated in comparable samples in the Netherlands, or in LASA pilot studies.[22,46]

Statistical analysis

The incidence rate was calculated as the number of events (MDD) divided by the total time in years that people were at risk in the sample. Cox proportional hazards regression models were conducted as main method for inferential statistics. In order to predict MDD from SUBD, participants who had MDD at follow-up were labeled as "cases". Those that remained chronic SUBD, recovered from SUBD or dropped-out (death or loss to follow-up) were all treated as "censored". In order to predict recovery from SUBD, participants that recovered from SUBD at follow-up were labeled as "cases". Participants that remained chronic SUBD, developed MDD or dropped-out of the study were all treated as "censored". Multiple imputation was performed in SPSS with 5 iterations (relative efficacy >95%) to optimize study power in multivariate analyses.[47] There was no marked difference between the original and imputed dataset regarding the means and standard deviations. Predictors with a $p \leq 0.20$ in bivariate analyses were included in multivariate analyses and analyzed through stepwise backward method analyses ($P_{out} \geq 0.05$). According to the TRIPOD-statement, backward stepwise selection procedures has come as the best modeling procedure to identify the strongest predictors.[48] The goodness of fit of both models was evaluated with the -2 Log Likelihood (-2LL) method yielding a chi-square. We compared the -2LL of the fitted model to the -2LL of the null model (no predictors) and evaluated changes in the -2LL during the process of backward stepwise elimination. Statistical analyses were performed with the Statistical Package for Social Sciences version 22.0 (SPSS).

Results

Baseline and follow-up characteristics of the SUBD sample are presented in Table 1. The mean (SD) age at baseline was 72.3 (7.9) years. Women predominated and accounted for 68.6%. N=50 (14.7%) participants had a prior diagnosis of major depression. The median (IQR) follow-up time of the entire study sample was 10.2 (5.5) years. The total number of person-years at risk was 3307.8 person-years.

Prognosis of SUBD

The largest proportion recovered from SUBD (N=153, 44.9%), another substantial part remained chronically SUBD (N= 138, 40.5%), and a minority of people developed MDD (N=50, 14.7%). From those developing MDD, 26% of respondents reported a previous episode of major depression, 32% reported a positive family history of major depression and 10% reported both. The median (IQR) time to recovery from SUBD was 2.8 (0.3) years. The median (IQR) time to onset of MDD was 5.7 (5.8) years. The incidence rate of MDD from late-life SUBD was 15.1 per 1000 person-years (95% CI: 11.3,19.8).

Predictors of MDD

Table 2 gives results of the Cox proportional hazards regression model. Fifteen putative predictors were preselected by bivariate analyses and included in multivariate analyses**.** In multivariate analyses (goodness of fit: χ^2=38.064, df=7, p<0.001), women, high neuroticism, more chronic diseases, high BMI, smoking and lack of social support remained stable predictors of MDD. These predictors were assessed for their cumulative effects of conversion to MDD. Table 3 shows point estimated hazard ratios with up-to-tenfold increased risks for MDD conversion if predictors were cumulatively added to the Cox regression equation. For example, it demonstrates that vulnerable people with SUBD, such as neurotic women with chronic diseases (HR: 3.6), are particularly at risk of converting to MDD in presence of bad lifestyle behaviors, such as smoking and high BMI (HR: 11.0), and lack of social support (HR: 23.6).

Predictors of recovery from SUBD

Table 4 gives results of the Cox proportional hazards regression model. Fifteen putative predictors were preselected and included in multivariate analyses (goodness of fit: χ^2=29.883, df=3, p<0.001). Men, low neuroticism, and low levels of pain predicted recovery from SUBD.

Additional information

Antidepressants were used at baseline by N=7 (4.6%) that recovered from SUBD, N=3 (2.2%) that remained chronically SUBD, and N=2 (4.0%) that developed MDD. A psychiatrist was consulted for treatment within 6 months before baseline by N=4 (2.6%) that recovered from SUBD, N=7 (5.1%) that remained chronically SUBD, and N=2 (4.0%) that developed MDD.

Table 1. Sample characteristics of SUBD at baseline and follow-up (N=341)

Predictors	Baseline		Follow-up					
	SUBD N=341, 100%		MDD N=50, 14.7%		Recovery N=153, 44.9%		Chronic SUBD N=138, 40.5%	
Vulnerability indicators	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age	72.3	7.9	71.0	7.3	71.8	7.7	73.3	8.1
Education	8.3	3.0	7.8	2.6	8.4	3.1	8.3	3.2
Neuroticism	10.6	6.1	12.6	6.0	8.8	5.9	11.8	5.9
Mastery	15.2	3.4	15.3	2.9	15.6	3.5	14.8	3.4
General cognitive functioning	26.9	2.6	27.0	2.5	27.2	2.1	26.5	3.1
Personal network size	13.1	7.6	11.6	8.3	13.9	7.8	12.8	7.1
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Women	234	68.6	41	82.0	95	62.1	98	71.0
Living in a city	215	63.0	30	60.0	93	60.8	92	66.7
Lack of partner	176	51.6	25	50.0	78	51.0	73	52.9
History of depression	50	14.7	13	26.0	20	13.1	17	12.3
Familial history of depression	95	27.9	16	32.0	42	27.5	37	26.8
Adverse early childhood event	128	37.5	22	44.0	49	32.0	57	41.3
Stress indicators	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
# Recent negative life events	1.2	1.0	1.5	1.1	1.1	1.0	1.3	1.1
Depressive symptoms	20.8	5.3	20.6	4.7	20.4	4.8	21.4	5.9
Anxiety symptoms	6.7	3.9	7.3	3.9	6.4	4.0	6.9	3.9
Sleep problems	7.1	2.2	7.5	2.1	6.8	2.3	7.2	2.2
Reported pain	6.6	1.7	6.8	1.8	6.3	1.5	6.8	1.7
Body Mass Index	27.4	4.6	28.8	4.0	27.0	4.2	27.4	5.2
# Chronic diseases	1.4	1.1	1.7	1.4	1.3	1.0	1.5	1.1
# Functional limitations	1.3	1.2	1.2	1.2	1.1	1.1	1.5	1.2
Instrumental support received	0.9	0.7	0.7	0.7	0.8	0.7	1.0	0.7
Instrumental support given	0.7	0.7	0.8	0.7	0.7	0.7	0.6	0.7
Emotional support received	1.7	0.7	1.8	0.7	1.6	0.8	1.7	0.7
Emotional support given	1.7	0.7	1.9	0.7	1.8	0.7	1.7	0.7
Loneliness	4.0	3.2	4.3	3.1	3.5	3.1	4.5	3.2
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Poor self-perceived health	104	30.5	19	38.0	42	27.5	43	31.2
Alcohol use								
Abstainer	87	25.5	13	26.0	28	18.3	46	33.3
Moderate	223	65.4	30	60.0	113	73.9	80	58.0
Excessive	31	9.1	7	14.0	12	7.8	12	8.7
Smoking	70	20.5	14	28.0	29	19.0	27	19.6

SUBD, subthreshold depression; #, number of; MDD, major depressive disorder; SD, standard deviation.

Table 2. Cox regression models for major depressive disorder from SUBD in later life

Predictors	Bivariate analyses[a]			Multivariate analyses[a]		
	HR	95% CI	*p*	HR	95% CI	*P*
Vulnerability indicators						
Age	1.00	0.96, 1.03	0.74			
Education	0.94	0.85, 1.04	0.24			
Neuroticism[b]	1.05	1.01, 1.10	**0.03**	1.05	1.01, 1.11	**0.03**
Mastery	1.00	0.92, 1.09	0.98			
General cognitive functioning	1.01	0.90,1.13	0.87			
Personal network size[b]	0.96	0.92, 1.01	0.10			
Women[b]	2.07	1.01, 4.26	**0.05**	2.26	1.08, 4.76	**0.03**
Living in a city	0.94	0.54, 1.66	0.84			
Lack of partner	0.97	0.55, 1.68	0.90			
History of depression[b]	2.01	1.07, 3.79	**0.03**			
Familial history of depression	1.15	0.63, 2.08	0.65			
Adverse early childhood event	1.35	0.76-2.37	0.31			
Stress indicators						
# Recent negative life events[b]	1.31	1.02, 1.68	**0.03**			
Depressive symptoms	1.00	0.94, 1.05	0.91			
Anxiety symptoms	1.04	0.97, 1.12	0.24			
Sleep problems[b]	1.09	0.97, 1.24	0.15			
Reported pain[b]	1.19	1.02, 1.39	**0.03**			
Body Mass Index[b]	1.07	1.01, 1.13	**0.02**	1.08	1.02,1,15	**0.01**
# Chronic diseases[b]	1.32	1.04, 1.67	**0.03**	1.48	1.14,1.91	**0.003**
# Functional limitations	0.99	0.78, 1.27	0.96			
Instrumental support received[b]	0.71	0.46, 1.10	0.12	0.55	0.33,0.91	**0.02**
Instrumental support given[b]	1.57	1.07-2.29	**0.02**	2.24	1.45,3.45	**<0.001**
Emotional support received[b]	1.34	0.88-2.05	0.18			
Emotional support given[b]	1.37	0.90-2.07	0.14			
Loneliness	1.04	0.96, 1.13	0.36			
Poor self-perceived health[b]	1.47	0.83, 2.61	0.19			
Alcohol						
Moderate	0.86	0.45, 1.65	0.76			
Excessive	1.53	0.61, 3.84	0.47			
Smoking[b]	1.59	0.86, 2.94	0.14	2.53	1.29,4.95	**0.007**

SUBD, subthreshold depression; #, number of; HR, hazard ratio; CI, confidence interval

[a] Cox proportional hazards regression analyses were conducted. Predictors were preselected from bivariate analyses ($p_{in} \leq 0.20$) and included in multivariate stepwise backward analyses ($p_{out} \geq 0.05$)

[b] Indicates a predictor with a p-value ≤0.20 in bivariate analyses

Bold type indicates significance, $p<0.05$

Table 3. Point estimated hazard ratios for cumulative predictors of MDD from SUBD

Predictors	Hazard Ratio[a]
Women (reference: men)	2.3
Women + Neuroticism[b]	2.8
Women + Neuroticism + # Chronic Diseases[b]	3.6
Women + Neuroticism + # Chronic Diseases + Body Mass Index (BMI)[b]	4.3
Women + Neuroticism + # Chronic Diseases + BMI + Smoking	11.0
Women + Neuroticism + # Chronic Diseases + BMI + Smoking + Inadequate Social Support[c]	23.6

SUBD, subthreshold depression; MDD, major depressive disorder; #, number of

[a] We filled in the Cox regression equation for cumulative predictors that were gained from multivariate analyses for MDD (Table 2)

[b] The presence of a continuous predictor was defined as the third quartile value (Q_3) of that predictor: $Q_{3\ neuroticism} = 15$; $Q_{3\ \#\ chronic\ diseases} = 2$; $Q_{3BMI} = 30$

[c] Inadequate social support was defined as a combination of $Q_{1\ instrumental\ support\ received} = 0.25$ and $Q_{3\ instrumental\ support\ given} = 1.1$

Table 4. Cox regression models for recovery from SUBD in later life

Predictors	Bivariate analyses[a]			Multivariate analyses[a]		
	HR	95% CI	*p*	HR	95% CI	*p*
Vulnerability indicators						
Age	0.99	0.97, 1.01	0.44			
Education	1.02	0.97, 1.08	0.36			
Neuroticism[b]	0.94	0.91, 0.96	**<0.001**	0.95	0.92, 0.98	**<0.001**
Mastery[b]	1.04	0.99, 1.09	0.13			
General cognitive functioning[b]	1.05	0.99, 1.12	0.14			
Personal network size[b]	1.02	1.00, 1.04	0.05			
Women[b]	0.68	0.49, 0.94	**0.03**	0.72	0.51, 0.99	**0.049**
Living in a city	0.87	0.63, 1.20	0.39			
Lack of partner	0.94	0.69, 1.30	0.72			
History of depression	0.84	0.53, 1.35	0.48			
Familial history of depression	0.97	0.68, 1.38	0.86			
Adverse early childhood event[b]	0.67	0.48, 0.95	**0.03**			
Stress indicators						
# Recent negative life events[b]	0.88	0.75, 1.03	0.11			
Depressive symptoms	0.98	0.95, 1.01	0.23			
Anxiety symptoms[b]	0.97	0.93, 1.01	0.12			
Sleep problems[b]	0.91	0.85, 0.99	**0.02**			
Reported pain[b]	0.84	0.75, 0.94	**0.002**	0.87	0.78,0.98	**0.02**
Body Mass Index[b]	0.97	0.94, 1.01	0.16			
# Chronic diseases[b]	0.90	0.77, 1.04	0.14			
# Functional limitations[b]	0.84	0.73, 0.96	**0.01**			
Instrumental support received	0.91	0.72, 1.15	0.41			
Instrumental support given	0.97	0.77, 1.23	0.82			
Emotional support received	0.89	0.71, 1.10	0.27			
Emotional support given	1.04	0.83, 1.30	0.75			
Loneliness[b]	0.93	0.88, 0.98	**0.008**			
Poor self-perceived health	0.84	0.59, 1.20	0.34			
Alcohol[b]						
Moderate	1.70	1.12, 2.57	**0.01**			
Excessive	1.18	0.60, 2.31	0.64			
Smoking	0.90	0.60, 1.35	0.62			

SUBD, subthreshold depression; #, number of; HR, hazard ratio; CI, confidence interval

[a] Cox proportional hazards regression analyses were conducted. Predictors were preselected from bivariate analyses ($p_{in} \leq 0.20$) and included in multivariate stepwise backward analyses ($p_{out} \geq 0.05$)

[b] Indicates a predictor with a p-value ≤0.20 in bivariate analyses

Bold type indicates significance, $p<0.05$

Discussion

The most important results from our study were that the majority of people with SUBD in later life recovered from SUBD (44.9%) or remained chronically in a state of SUBD (40.5%). A substantial minority of people affected with SUBD subsequently developed MDD (14.7%). However, the found incidence rate of MDD from SUBD in later life (15.1 per 1000 person-years) is twice the incidence rate of MDD from the general older population (7.0 per 1000 person-years).[49] Despite the fact that our study confirms previous findings that late-life SUBD is an at risk state for MDD, we had expected more conversions to MDD based on current literature (8-10% per year).[5] A possible explanation for fewer conversions found in our study may be that 3-year time intervals are insufficient to detect short episodes of MDD, risking an underestimation of the true incidence of MDD, instead of studies that focused on short-term prognosis with more frequent measurements. On the other hand, our research question focused on the long-term follow-up and predictors of long-term outcome. The median onset time at which MDD developed from SUBD in our study was six years, suggesting that previous studies with shorter follow-up may likely yield more inaccurate and pessimistic outcomes of SUBD.

Using rich data from a well-characterized longitudinal study of ageing, we were in a unique position to investigate a wide array of risk factors for MDD, representing both vulnerability and stress related factors. The unrevealed risk factors for MDD from SUBD in this study resemble known risk factors for MDD from the general population, such as being women, high neuroticism, more chronic diseases, bad lifestyle behaviors (smoking, high BMI) and lack of social support.[30,50] In addition, we showed that people with SUBD in presence of cumulative and largely modifiable predictors were at increased risk of MDD conversion, all important for indicated prevention programs. For example, vulnerable neurotic women with chronic diseases had nearly sevenfold increased risk of conversion to MDD if modifiable stressors were also present, such as smoking, overweight and lack of social support. Conversely, people who recovered from SUBD may be characterized by lacking vulnerability, such as being men and having low levels of neuroticism. Also, those who recovered reported less pain, suggesting that experiencing pain may be an obstacle for older people with SUBD to recover.

An important clinical implication is that further targeting indicated prevention to people with SUBD in later life at very high risk seems feasible and necessary. Depression in later life is harmful and has been associated with adverse health outcomes, such as disability,[8] excess mortality,[9] and an increased risk of dementia.[51] The majority of people with late-life SUBD spontaneously recovers, therefore 'watchful waiting' seems adequate in this group, especially in men and people with low neuroticism. Clinicians might also pay attention

to pain and its management, as our results suggest that pain may be an obstacle to recover from SUBD. People with SUBD that are at (very) high risk of conversion to MDD may be selected for indicated prevention programs, including low cost psychological interventions.[52] Furthermore, clinicians should focus their treatments on the adequate management of comorbid chronic diseases, influence bad lifestyle behaviors - stop smoking and increase physical activity to reduce weight - and improve social support if necessary. These recommendations has also been reported by others.[53]

Our study has several strengths. To our knowledge, this is the first study that was able to include up to 17-years follow-up on SUBD. Second, we performed the same two-stage screening procedure to identify those with SUBD and MDD, employing both an established symptom rating scale and diagnostic interview, yielding accurate estimates of the long-term development of SUBD.

An important limitation of our study was the sample size. In particular the number of MDD events was small (N= 50), relative to the number of predictor variables we wanted to analyze. We addressed this limitation by preselecting variables from bivariate analyses and include them in multivariate analyses. This reduced the number of predictor variables from twenty-nine to fifteen. Multinomial regression analyses were performed as a sensitivity check, because of a small chance that we found some spurious findings (type one error) due to multiple comparisons. We observed that the results of multinomial regression analyses were largely in agreement with those of the Cox regression models, but that only the associations of experiencing pain and received instrumental support were removed from the final model. Furthermore, time to onset of MDD may be potentially overestimated because both MDD could have started more earlier and short MDD episodes might have been missed before the past-year diagnostics. In the design of the study we deliberately chose not to investigate risk factors associated with the group that remained chronically SUBD. However, considering the size of the group (40.5%), there might also be an important opportunity here to decrease the overall health burden of depression. More proper research is needed to elucidate the risk factors that are associated with the group that remained chronically SUBD.

In conclusion, SUBD in later life is a highly prevalent and heterogeneous condition. Although older people with SUBD are clearly at risk of developing MDD, the majority did not. Further targeting indicated prevention to those at very high risk is feasible, given the risk factors found. More precise identification of older adults in whom preventative intervention is likely successful reduces both costs and the numbers of older people exposed to intervention, while simultaneously improving the number needed to treat in preventative psychiatry.

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Chapter 6

A six-year prospective study of the prognosis and predictors in patients with late-life depression

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Abstract

Objective: To examine the six-year prognosis of patients with late-life depression and to identify prognostic factors of an unfavorable course.

Method: The Netherlands Study of Depression in Older persons (NESDO) is a multi-site naturalistic prospective cohort study with six-year follow-up. 378 clinically depressed patients according to DSM-IV-TR criteria and 132 non-depressed comparisons were included at baseline between 2007-2010. Depression was measured by the Inventory of Depressive Symptoms at six-month intervals and a diagnostic interview at two-year and six-year follow-up. Multinomial regression and mixed model analyses were both used to identify depression-related clinical, health and psychosocial prognostic factors of an unfavorable course.

Results: Among depressed patients at baseline, 46.8% were loss to follow-up, 15.9% had an unfavorable course, i.e. chronic or recurrent, 24.6% had partial remission, and 12.7% had full remission, at six-year follow-up. The relative risk (RR) of mortality in depressed patients was 2.5 (95%-CI:1.26-4.81) when compared with non-depressed comparisons. An unfavorable course of depression was associated with a younger age of depression onset, higher symptom severity of depression, pain, neuroticism, and loneliness at baseline. Additionally, partial remission was associated with chronic diseases, and loneliness at baseline when compared with full remission.

Conclusions: The long-term prognosis of late-life depression is poor with regard to mortality and course of depression. Chronic diseases, loneliness, and pain may be used as putative targets for optimizing prevention and treatment strategies of relapse and chronicity.

Introduction

Late-life depression is a complex and heterogeneous disorder, often accompanied by an unfavorable prognosis.[1] It has been associated with a chronic course,[2] a higher risk of subsequent development of cognitive impairment or dementia,[3] and premature death.[4] Although late-life depression can be treated effectively, relapse and recurrence as well as chronicity are a major problem in daily practice. Studies on the long-term prognosis of late-life depression are required to inform clinicians and to identify prognostic factors that may contribute to the improvement of treatment strategies and relapse prevention.

An unfavorable prognosis of late-life depression has been demonstrated in both community samples,[5–8] and clinical samples.[9–14] Beekman et al. (2002) studied the six-year course of community-dwelling older adults with late-life depression, using both diagnostic interviews and self-reports, and found that 32% had a severe chronic course and 44% an unfavorable but fluctuating course, whereas only 23% showed remission.[6] In our previous two-year follow-up study of the Netherlands Study of Depression in Older persons (NESDO), we found that nearly 50% of the clinically depressed patients still had a depression diagnosis, and 61% had a chronic course of depressive symptoms.[13] It is known that depression in older adults is more likely to have a chronic or chronic-relapsing course compared to younger adults.[2,15] Since meta-analyses of treatment studies have demonstrated equal efficacy of antidepressants among all ages,[16] suboptimal maintenance treatment may be an explanation for the less favorable prognosis in older adults. Also, some specific depressive syndromes occur more often in later life, such as the depression-executive dysfunction syndrome with apathy,[17] which has particularly been linked to a poor outcome.[18,19]

Currently, there has been an increasing interest to identify distinct long-term trajectories of depressive symptoms using latent class analyses. Hybels et al. (2016) identified four trajectory classes in a clinical sample of depressed older adults after three-years of follow-up, including a quick recovery class (43%), a persistent moderate symptom class (27%), a persistent high symptom class (15%), and a slow recovery class (15%).[12] Higher perceived stress and lower social support were associated with the persistent high symptom class.[12] These trajectories have proved to be useful in obtaining a better insight in the course of late-life depression, for example, by distinguishing a fast recovery class from a slow recovery class.[12,20] However, its use for clinicians may be limited, for they rely on a depression diagnosis for the management of depression, not on depressive symptoms only.

Multiple factors from different domains of functioning contribute to the onset and prognosis of depression.[21] For clinical purpose, prognostic factors may be assigned to a depression-related clinical domain, a health and lifestyle domain, and a psychosocial domain. Several factors from these domains have been associated with an unfavorable course of depression, including comorbid anxiety,[22] sleep problems,[23] chronic diseases,[13,15] functional limitations,[24] pain,[25] loneliness,[26] lack of social support,[12] childhood trauma,[27] and neuroticism.[28] Whether these factors are also associated with the prognosis of depression on the long-term remains to be explored.

The aim of the present study was twofold. First, the long-term prognosis of late-life depression was examined, in terms of both main reasons for attrition and course types, in clinically depressed patients over six-years. Second, prognostic factors of long-term course types were identified. We hypothesized that the long-term prognosis of late-life depression is poor, with a high mortality rate and an unfavorable course, including recurrence and chronicity, in most patients.

Methods

Study Design

The Netherlands Study of Depression in Older persons (NESDO) is a multi-site prospective cohort study designed to examine the course and consequences of depressive disorders in older adults (≥60 years). Sampling procedures have been previously described in detail.[29] In short, data collection of the baseline measurement took place between 2007 and 2010. Depressed patients were recruited in five regions in the Netherlands from both mental health care facilities and general practitioners. Non-depressed comparisons were recruited from general practitioners and were included if they had no lifetime diagnosis of depression. Participants were excluded when they had a dementia diagnosis, or were suspected for dementia based on clinician's judgment. Follow-up assessments by means of a face-to-face interview were performed two-years,[13] and six-years after baseline using the same measurement instruments as at baseline. Additionally, postal assessments were performed every six-months, including a questionnaire on self-reported depressive symptoms. Well-trained research assistants conducted the interviews. All interviews were audio taped and quality controlled. The research coordinator regularly evaluated interviews on the basis of their audiotapes. Question wording and probing behavior of interviewers were regularly monitored by checking a random selection of each interviewer. Written informed consent was obtained from all participants. NESDO' study protocol has been approved centrally by the Ethical Review Board of the VU University Medical Center, and subsequently by the ethical review boards of the Leiden University Medical Center, University Medical Center Groningen, and the Radboud university medical center Nijmegen.

Sample

At baseline, NESDO included 378 depressed patients, having major depressive disorder (n=265), dysthymia (n=6), double depression (n=94) (major depression and dysthymia) or minor depression (n=13) according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR criteria),[30] and 132 non-depressed comparisons, aged ≥ 60 years.[13] Depressed patients did not differ from non-depressed comparisons with respect to mean age and sex, but depressed patients had less education, were more often divorced or widowed, and had lower cognitive functioning. From the 510 respondents at baseline, 401 were retained in the two-year follow-up assessment with an overall attrition rate of 21.4%.[13]

Measurements

Depression

The DSM-IV-TR-diagnosis of major depression, dysthymia and minor depression was assessed with the Composite Interview Diagnostic Instrument (CIDI, WHO, version 2.1) at two- and six-year of follow-up.[30] Severity of depressive symptoms was measured by a postal assessment every six months as a continuous variable with the Inventory of Depressive Symptoms (IDS),[31] which is a 30-item self-report scale that was developed to assess all core criterion diagnostic depressive symptoms. The IDS scores range between 0 and 84 with higher scores indicating more severe depression. An IDS score < 14 was defined as no depression.[32] The scale has acceptable psychometric properties in depressed outpatients,[31] and depressed inpatients.[32] Cronbach's alpha for the IDS in our sample was 0.83.

Course types

The course types were categorized according to the two-year and six-year measurement into: a) full remission, b) partial remission, c) recurrent, and d) chronic, using both the symptom severity level (according to the IDS) and diagnosis of depression (according to the DSM-IV-TR). Full remission was defined as the absence of a depression diagnosis at six-year follow-up, combined with an IDS score < 14 at six-year follow-up (at measurement cycles 12 and 13, thereby covering six months). Partial remission was defined as the absence of a depression diagnosis at six-year follow-up, but with an IDS score ≥ 14 at six-year follow-up (at measurement cycle 12 and 13). Absence of a depression diagnosis at two-year, but presence of a diagnosis at six-year was labeled as 'recurrent'. Presence of a depression diagnosis both at two- and six-year follow-up was labeled as 'chronic'. The last two categories (recurrent and chronic) were based on diagnosis of depression according to the CIDI only.

Prognostic factors

Demographics were assessed using standard questions and included sex, age, and educational level (years). The following *depression-related clinical factors* were included: previous episode of depression, age of onset of depression and comorbid anxiety diagnosis (y/n) were assessed by the CIDI, severity of depressive symptoms was assessed by the IDS,[31] severity of anxiety symptoms was assessed by the Beck Anxiety Index (BAI),[33] global cognitive functioning was assessed by the Mini Mental State Examination (MMSE),[34] apathy was assessed by the Apathy Scale (AS),[35] sleep problems was assessed by the Women's Health Initiative Insomnia Rating Scale (WHIIRS),[36] use of antidepressants and frequent use of benzodiazepines were assessed by inspection of the medication. The following health and *lifestyle factors* were included: chronic physical diseases were self-reported and assessed by the LASA Questionnaire (LAPAQ),[37]

functional limitations were assessed by the WHO-Disability Assessment Scale II (WHODAS 2.0),[38] metabolic syndrome was assessed by the original ATP-III criteria,[39] chronic pain was assessed by the Chronic Graded Pain Scale (CPGS),[40] body-mass-index was measured by weight (kg)/squared height (m^2), physical activity was assessed by the International Physical Activities Questionnaire (IPAQ) and dichotomized (low versus moderate/high),[41] smoking was assessed by asking current smoking behavior (y/n), and alcohol use was assessed by Alcohol Use Disorders Identification (AUDIT).[42] The following *psychosocial factors* were included: neuroticism was assessed by the NEO-Five Factor Inventory (NEO-FFI),[43] childhood trauma was assessed by the Netherlands Mental Health Survey and Incidence Study (NEMESIS) Questionnaire,[44] partner status (y/n) was asked, loneliness was assessed by the Rasch-Type Loneliness Scale (RTLS),[45] social support was assessed by the Close Person Inventory and dichotomized (poor: < 2 confidents versus good: ≥ 2 confidents),[46] and recent life events were assessed by the Brugha Questionnaire.[47]

Statistical Analyses

First, descriptive analyses were used to describe attrition and its determinants in the patient group (eTable 1). For both the patient group and non-depressed comparison group, attrition rates were calculated by dividing the proportion of respondents that were loss to follow-up with the total number of respondents at baseline. Subsequently, bivariate and multivariate logistic regression analyses were used to identify determinants of attrition (eTable 2). Second, study sample characteristics were described according to the 'course of late-life depression', in which the groups 'recurrent' and 'chronic' were combined to ensure equal group sizes for the purpose of subsequent statistical analyses (Table 1).

A correlation matrix was derived for the independent variables to rule out multicollinearity. A Pearson correlation cutoff of 0.70 was used to determine whether substantial correlation was present, and whether variables had to be left out of subsequent analysis. No correlation > 0.70 was found between all the independent variables. The highest correlations observed were between BAI and neuroticism (0.52), BAI and WHODAS 2.0 (0.45). Also, the correlations between the independent variables at baseline and the dependent variable IDS at baseline, and at two-year and six-year follow-up, were retrieved. At baseline, none of the variables was correlated with IDS at > 0.70. The highest correlations observed were between IDS and WHODAS 2.0 (0.69), IDS and BAI (0.56), and IDS and neuroticism (0.54). Bivariate multinomial regression analyses were performed to investigate the association between each prognostic factor and 'course of late-life depression', using 'full remission' as reference group (Table 2). An additional analysis was performed using 'partial remission' as reference group for the comparison with a chronic/recurrent (unfavorable) course.

To overcome the study's statistical power problem, multivariate analyses were performed using Linear Mixed Models with the longitudinally measured 'symptom severity of depression' (IDS) as dependent variable (Table 3). First, group wise multivariate analyses were conducted for each of the three separate domains. Subsequently, the final multivariate model contained all prognostic factors that were associated with IDS at $p<.05$ from the group wise multivariate analyses. The goodness of fit for all multivariate models was evaluated with the -2 Log Likelihood (-2LL) method by comparing the fitted fixed-effects models to the model with no predictors (null model). We evaluated changes in the -2LL between the null model and each fitted fixed-effects model. Analyses were performed using IBM SPSS 22.0.

Results

Attrition of NESDO

Figure 1 contains the flowchart of NESDO. From the 510 respondents at baseline, 299 participated in the six-year follow-up assessment with an overall attrition rate of 41.4%. The attrition rate between two- and six-year follow-up was 25.4%. The attrition rates for the patient and comparison group differed at 46.8% and 25.8%, respectively. The most important reasons for attrition in the patient group were mortality (16.4%) and mental reasons (15.1%), mainly cognitive impairment, whereas the most important reason for attrition in the non-depressed comparison group was refusal (9.1%). A total of seventy participants (13.7%) died during six-year follow-up, including sixty-two depressed patients and eight non-depressed comparisons. The relative risk of mortality among depressed patients was 2.47 time (95% CI: 1.26-4.81) higher when compared with non-depressed comparisons, $\chi^2(1) = 8.84$, p=.003.

Among depressed patients, attrition was the same for men and women, $\chi^2(1) = 0.78$, p=.38 (eTable 1). In bivariate analyses (eTable 2), determinants of attrition in the patient group were higher age (OR: 1.08, 95%-CI: 1.05-1.11), less education (OR: 0.93, 95%-CI: 0.87-0.98), a higher age of onset of depression (OR: 1.01, 95%-CI: 1.00-1.02), worse cognitive functioning (OR: 0.79, 95%-CI: 0.71-0.88), and less physical activity (OR: 2.01, 95%-CI: 1.28-3.15). In multivariate analyses, age (OR: 1.06, 95%-CI: 1.03-1.09) and global cognitive functioning (OR: 0.83, 95%-CI: 0.75-0.95) remained significantly associated with attrition in the patient group.

Prognosis of late-life depression

Among the total of 378 depressed patients at baseline, 177 (46.8%) were loss to follow-up, 60 (15.9%) had a recurrent or chronic depression, 93 (24.6%) had a partial remission and only 48 (12.7%) had a full remission at six-year follow-up. Of those with a full remission at six years, 43.8% reached this after two years.

Table 1 shows the characteristics from 201 clinically depressed patients who were able to participate in the study over the full six years according to their course type. This sample consisted of 137 (68.2%) women, and the mean age of the sample was 69.0 (SD: 6.5) years. Sixty (29.9%) depressed patients had an unfavorable course type (8.0% recurrent, 21.9% chronic), 93 (46.3%) had a partial remission, and 48 (23.9%) had a full remission. The symptom severity levels of depression (IDS) at six-month intervals according to the prognosis of depressed patients after six-year follow-up is shown in Figure 2.

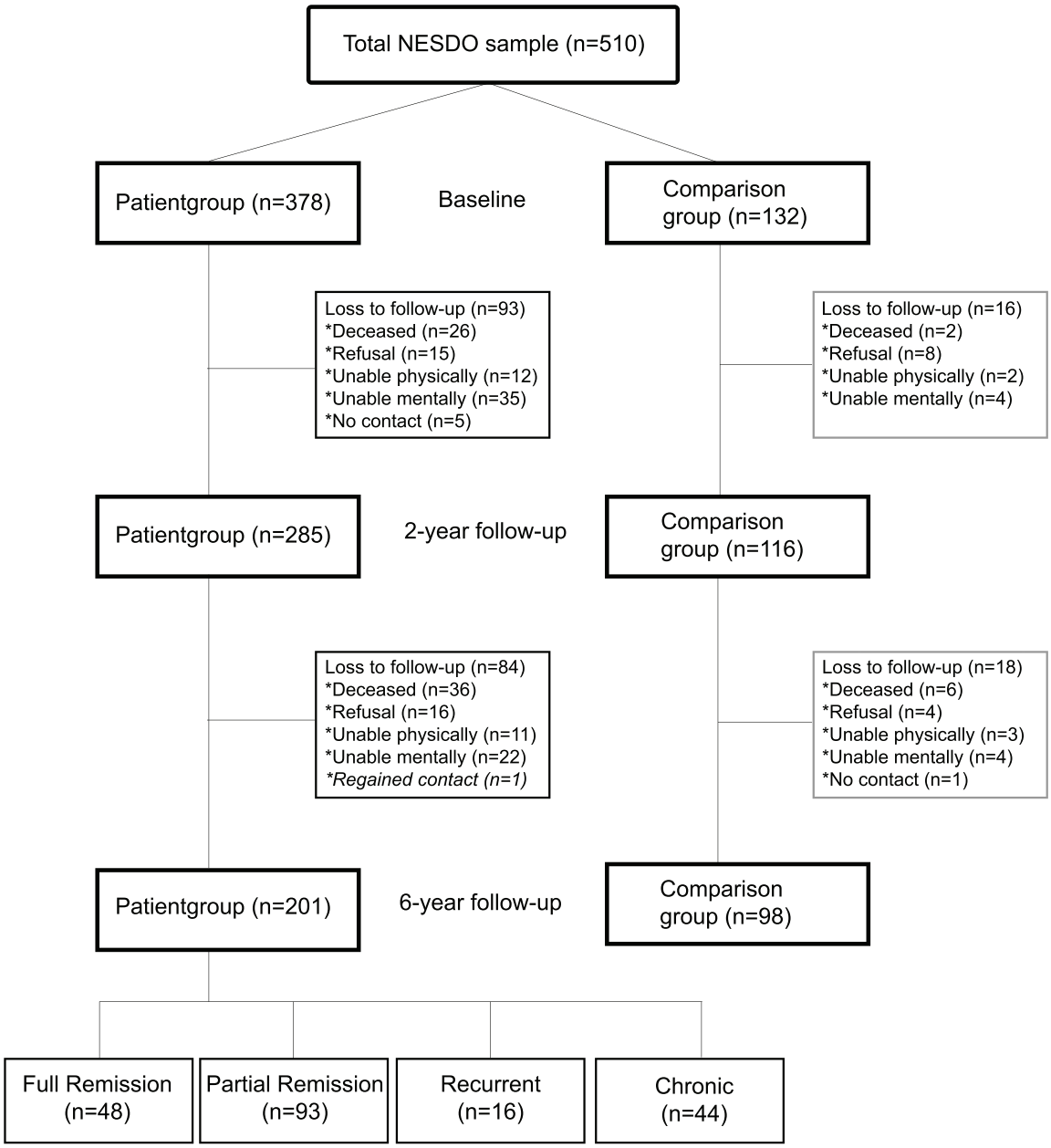

Figure 1. Flowchart of NESDO and long-term prognosis of late-life depression

Prognostic factors

In Table 2, results from bivariate analyses demonstrate that the depression-related clinical factors: younger age of onset of depression, higher severity of depression, higher severity of anxiety, and more apathy; the health and lifestyle factors: chronic diseases, functional limitations, and chronic pain; and the psychosocial factors: neuroticism and loneliness were all associated with an unfavorable course type as compared to full remission. As compared to full remission, partial remission was only associated with chronic diseases and loneliness, and not with any of the depression-related clinical factors. As compared to partial remission, an unfavorable course type was associated with a younger age of onset of depression, higher severity of depression, a comorbid anxiety disorder, higher severity of anxiety, use of antidepressants, functional limitations, less physical activity, less alcohol use, and neuroticism.

From multivariate longitudinal analyses (Table 3), a younger age of onset of depression, higher severity of depression, chronic pain, neuroticism, and loneliness at baseline were significantly associated with higher levels of depression over the six-year follow-up.

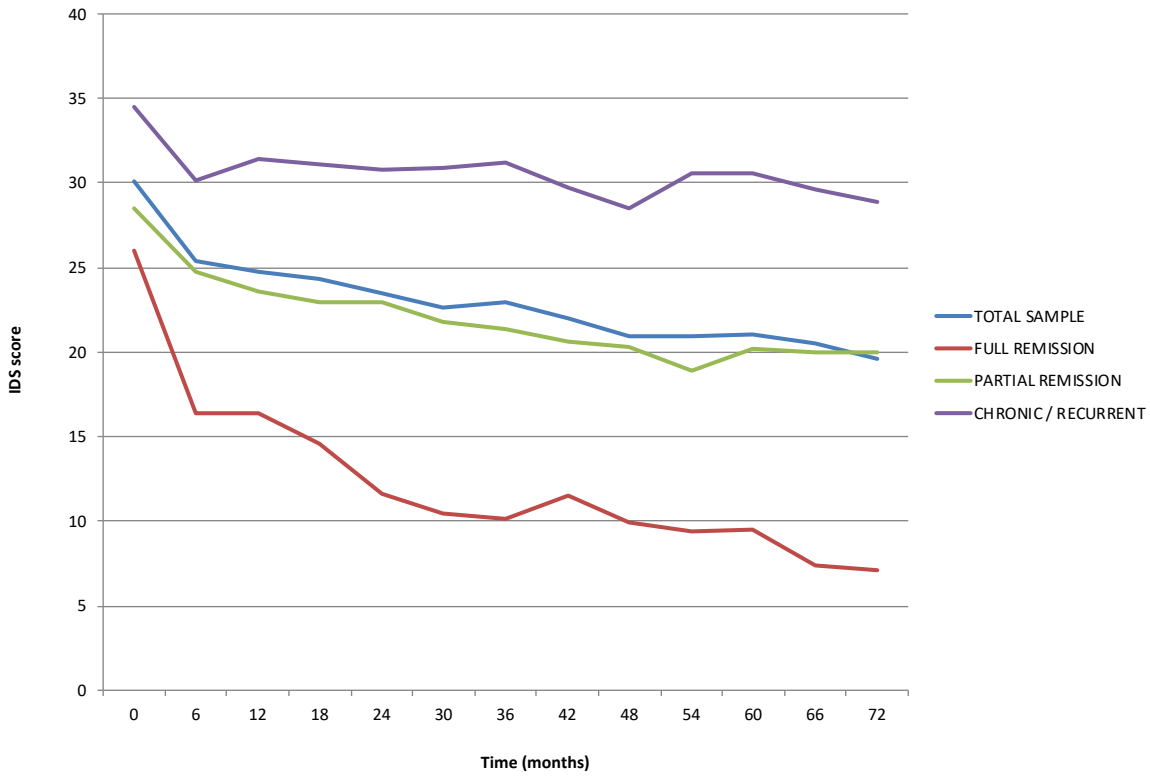

Figure 2. Symptom severity levels of depression (IDS) at six-month intervals according to the prognosis of depressed patients after six-year follow-up

Table 1. Characteristics of N=201 depressed patients at baseline and according to their course type of late-life depression at follow-up

Prognostic factors
Demographics
Women, N (%)
Age, years, mean (SD)
Education, years, mean (SD)
Depression-related clinical factors
Previous episode depression, yes, N (%)
Age of onset of depression, mean (SD)
Severity depressive symptoms, mean (SD)
Comorbid anxiety diagnosis, yes, N (%)
Severity anxiety symptoms, mean (SD)
Global Cognitive Functioning, mean (SD)
Apathy, mean (SD)
Sleep problems, mean (SD)
Use of antidepressants, yes, N (%)
Frequent use of benzodiazepines, yes, N (%)
Health and lifestyle factors
Chronic diseases, mean (SD)
Functional Limitations, mean (SD)
Metabolic syndrome, original ATP III criteria, yes, N (%)
Chronic Pain, yes, N (%)
Body-Mass-Index, mean (SD)
Physical activity, low, N (%)
Smoking, yes, N (%)
Alcohol, AUDIT, median (IQR)
Psychological and social factors
Neuroticism, mean (SD)
Childhood Trauma Index, mean (SD)
Partner, no, N (%)
Loneliness, mean (SD)
Social support, poor, N (%)
Recent life events, mean (SD)

SD = standard deviation; IQR = interquartile range; AUDIT = Alcohol Use Disorders Identification Test

Baseline	Six-year follow-up, course types		
Total N=201	Full remission N=48	Partial remission N=93	Recurrent or Chronic N=60
137 (68.2)	28 (58.3)	66 (71.0)	43 (71.7)
69.0 (6.5)	68.4 (5.9)	69.5 (6.8)	68.5 (6.5)
10.9 (3.5)	10.8 (3.1)	10.8 (3.4)	11.0 (4.0)
175 (90.2)	41 (87.2)	80 (90.9)	54 (91.5)
46.3 (19.7)	48.4 (18.3)	49.1 (18.5)	40.5 (21.4)
29.7 (12.5)	26.0 (13.6)	28.5 (10.2)	34.5 (13.6)
79 (39.3)	17 (35.4)	30 (32.3)	32 (53.3)
16.8 (10.7)	14.3 (10.6)	15.6 (9.2)	20.6 (12.1)
28.1 (1.6)	28.1 (1.5)	28.3 (1.4)	27.8 (2.0)
16.8 (5.3)	15.3 (5.2)	17.1 (5.4)	17.5 (5.2)
10.9 (5.2)	11.0 (5.7)	10.6 (5.1)	11.3 (5.1)
145 (72.9)	37 (78.7)	58 (63.0)	50 (83.3)
73 (36.3)	20 (41.7)	29 (31.2)	24 (36.3)
2.1 (1.5)	1.5 (1.0)	2.1 (1.5)	2.5 (1.8)
25.0 (12.3)	23.5 (11.9)	23.4 (11.2)	28.6 (13.7)
61 (30.3)	11 (22.9)	32 (34.4)	18 (30.0)
111 (55.5)	23 (47.9)	48 (51.6)	40 (67.8)
26.1 (4.3)	25.1 (3.7)	26.3 (4.2)	26.6 (4.8)
47 (24.1)	13 (28.3)	15 (16.7)	19 (32.2)
47 (23.4)	10 (20.8)	24 (25.8)	13 (21.7)
2 (4)	2 (4)	3 (5)	0 (3)
39.1 (6.2)	37.1 (5.9)	38.5 (4.9)	41.7 (7.4)
1.0 (1.2)	0.9 (1.1)	1.0 (1.1)	1.2 (1.3)
95 (47.3)	20 (41.7)	48 (51.6)	27 (45.0)
6.6 (3.5)	4.8 (3.3)	7.0 (3.4)	7.5 (3.3)
96 (48.0)	23 (48.9)	44 (47.3)	29 (48.3)
1.8 (1.3)	1.6 (1.3)	1.9 (1.4)	1.8 (1.3)

Table 2. Prognostic factors associated with long-term course types of late-life depression from bivariate analyses using multinomial logistic regression

	Partial remission (ref: full remission)			
Prognostic factors	**OR**	**95% CI**	**Wald χ^2**	**p-value**
Demographics				
Women	1.75	(0.84-3.62)	2.25	.13
Age	1.03	(0.97-1.08)	0.89	.35
Education	1.00	(0.90-1.11)	0.00	.99
Depression-related clinical factors				
Previous episode depression, yes	1.46	(0.48-4.50)	0.44	.51
Age of onset of depression	1.00	(0.98-1.02)	0.04	.84
Severity depressive symptoms	1.02	(0.99-1.05)	1.36	.24
Comorbid anxiety diagnosis, yes	0.87	(0.42-1.81)	0.14	.71
Severity anxiety symptoms	1.01	(0.98-1.05)	0.46	.50
Global Cognitive Functioning	1.08	(0.87-1.34)	0.45	.50
Apathy	1.07	(1.00-1.14)	3.36	.067
Sleep problems	0.99	(0.92-1.06)	0.17	.68
Use of antidepressants, yes	0.46	(0.20-1.04)	3.45	.063
Use of benzodiazepines, yes	0.63	(0.31-1.31)	1.53	.22
Health and lifestyle factors				
Chronic diseases	1.42	(1.08-1.87)	6.15	.013
Functional Limitations	1.00	(0.97-1.03)	0.00	.95
Metabolic syndrome, yes	1.77	(0.80-3.92)	1.95	.16
Chronic Pain, yes	1.16	(0.58-2.33)	0.17	.68
Body-Mass-Index	1.08	(0.98-1.18)	2.57	.11
Physical activity, low	0.51	(0.22-1.19)	2.45	.12
Smoking, yes	1.32	(0.57-3.05)	0.43	.51
Alcohol use	1.05	(0.95-1.16)	0.78	.38
Psychological and social factors				
Neuroticism	1.04	(0.98-1.10)	1.53	.22
Childhood Trauma Index	1.11	(0.81-1.52)	0.39	.53
Partner, no	0.67	(0.33-1.35)	1.25	.26
Loneliness	1.20	(1.08-1.34)	10.78	.001
Social support, poor	0.94	(0.46-1.89)	0.03	.86
Recent life events	1.24	(0.95-1.63)	2.45	.12

OR = odds ratio; CI = confidence interval; degrees of freedom for Wald χ^2 statistic = 1.

	Recurrent or Chronic (ref: full remission)				Recurrent or Chronic (ref: partial remission)			
	OR	95% CI	Wald χ^2	p-value	OR	95% CI	Wald χ^2	p-value
	1.81	(0.81-4.03)	2.09	.15	1.04	(0.51-2.12)	0.01	.93
	1.00	(0.94-1.06)	0.01	.95	0.98	(0.93-1.03)	0.88	.35
	1.02	(0.92-1.14)	0.15	.70	1.02	(0.93-1.12)	0.22	.64
	1.58	(0.45-5.54)	0.51	.47	1.08	(0.34-3.48)	0.02	.90
	0.98	(0.96-1.00)	4.11	.043	0.98	(0.96-0.99)	6.59	.010
	1.06	(1.02-1.10)	11.27	.001	1.04	(1.01-1.07)	8.07	.005
	2.08	(0.96-4.54)	3.41	.065	2.40	(1.23-4.68)	6.60	.010
	1.06	(1.02-1.10)	7.68	.006	1.04	(1.01-1.08)	6.99	.008
	0.90	(0.72-1.13)	0.83	.36	0.84	(0.69-1.02)	3.16	.076
	1.08	(1.00-1.17)	4.24	.040	1.01	(0.95-1.08)	0.20	.66
	1.01	(0.94-1.09)	0.12	.73	1.03	(0.97-1.10)	0.73	.39
	1.35	(0.51-3.58)	0.37	.55	2.93	(1.32-6.52)	6.94	.008
	0.93	(0.43-2.02)	0.03	.86	1.47	(0.75-2.90)	1.25	.26
	1.65	(1.23-2.21)	10.99	.001	1.16	(0.94-1.43)	1.95	.16
	1.04	(1.00-1.07)	4.34	.037	1.04	(1.01-1.07)	6.29	.012
	1.44	(0.60-3.44)	0.68	.41	0.82	(0.41-1.64)	0.32	.57
	2.29	(1.04-5.03)	4.25	.039	1.97	(0.99-3.90)	3.83	.050
	1.10	(1.00-1.21)	3.50	.061	1.02	(0.95-1.10)	0.23	.63
	1.21	(0.52-2.80)	0.19	.66	2.38	(1.09-5.17)	4.75	.029
	1.05	(0.42-2.66)	0.01	.92	0.80	(0.37-1.72)	0.34	.56
	0.89	(0.77-1.03)	2.43	.12	0.85	(0.75-0.97)	5.90	.015
	1.14	(1.06-1.22)	12.90	<.001	1.09	(1.03-1.16)	8.98	.003
	1.26	(0.90-1.76)	1.83	.18	1.14	(0.87-1.50)	0.88	.35
	0.87	(0.41-1.88)	0.12	.73	1.30	(0.68-2.50)	0.64	.43
	1.26	(1.11-1.42)	13.58	<.001	1.05	(0.94-1.16)	0.75	.39
	0.98	(0.46-2.10)	0.00	.95	1.04	(0.54-2.00)	0.02	.90
	1.17	(0.88-1.57)	1.13	.29	0.95	(0.74-1.20)	0.21	.65

Table 3. Prognostic factors associated with higher symptom levels of depression during six years from bivariate and multivariate linear mixed models analyses

	Bivariate models		
Prognostic factors	**β (SE)**	**p-value**	**df.**
Demographics			
Women	2.24 (1.60)	.16	198
Age	-0.03 (0.12)	.79	199
Education	0.04 (0.22)	.87	199
a) Depression-related clinical factors			
Previous episode depression, yes	7.70 (2.52)	.003	191
Age of onset of depression	-0.16 (0.04)	<.001	193
Severity depressive symptoms	0.55 (0.05)	<.001	198
Comorbid anxiety diagnosis, yes	3.73 (1.51)	.014	198
Severity anxiety symptoms	0.51 (0.06)	<.001	189
Global Cognitive Functioning	-0.57 (0.46)	.22	201
Apathy	0.69 (0.14)	<.001	188
Sleep problems	0.57 (0.14)	<.001	190
Use of antidepressants, yes	-0.52 (1.70)	.76	196
Use of benzodiazepines, yes	-0.25 (1.56)	.87	198
a) Health and lifestyle factors			
Chronic diseases	2.70 (0.45)	<.001	198
Functional Limitations	0.41 (0.05)	<.001	192
Metabolic syndrome, yes	3.92 (1.61)	.015	199
Chronic Pain, yes	7.80 (1.39)	<.001	198
Body-Mass-Index	0.81 (0.17)	<.001	201
Physical activity, low	-1.41 (1.79)	.43	193
Smoking, yes	0.92 (1.77)	.60	198
Alcohol use	-0.47 (0.21)	.025	196
a) Psychological and social factors			
Neuroticism	0.89 (0.11)	<.001	188
Childhood Trauma Index	1.56 (0.64)	.015	198
Partner, no	1.15 (1.50)	.44	198
Loneliness	1.18 (0.21)	<.001	188
Social support, poor	-0.19 (1.50)	.90	197
Recent life events	0.53 (0.56)	.35	198

β = regression coefficient; SE = standard error; df. = degrees of freedom, rounded to ones; p-values for the regression coefficients were generated with t-tests
Multivariate group wise analyses contains factors that were associated with p<0.05 in bivariate analyses, for each domain (a-c); The final multivariate model contains all factors that were associated with p<0.05 in the multivariate group wise analyses (a-c); goodness of fit: model a ($\chi^2(7) = 2370.073$, p<.001), model b ($\chi^2(6) = 607.702$, p<.001), model c ($\chi^2(3) = 956.429$, p<.001), final model ($\chi^2(10) = 2042.444$, p<.001)

	Multivariate models, group wise			Multivariate model, final		
	β (SE)	p-value	df.	β (SE)	p-value	df.
	group wise model a					
	-0.18 (2.19)	.93	165			
	-0.08 (0.03)	.017	165	-0.06 (0.03)	.040	166
	0.40 (0.06)	<.001	167	0.32 (0.07)	<.001	168
	0.88 (1.23)	.48	165			
	0.22 (0.07)	.002	168	0.11 (0.07)	.11	170
	0.30 (0.12)	.011	166	0.15 (0.12)	.20	166
	-0.09 (0.13)	.48	165			
	group wise model b					
	1.43 (0.43)	.001	187	0.68 (0.39)	.084	165
	0.25 (0.06)	<.001	187	-0.05 (0.06)	.46	168
	-0.68 (1.52)	.66	188			
	4.22 (1.32)	.002	188	2.60 (1.21)	.033	167
	0.46 (0.17)	.009	189	0.23 (0.14)	.12	167
	-0.14 (0.18)	.43	186			
	group wise model c					
	0.73 (0.11)	<.001	185	0.24 (0.12)	.043	167
	0.81 (0.55)	.15	184			
	0.70 (0.20)	.001	185	0.39 (0.18)	.036	166

Discussion

The most important conclusion to be drawn from this study among depressed older patients is that the long-term prognosis for this group is poor in terms of mortality and course of depression. Attrition in the patient group was almost twice as high as in the comparison group. During six-years of follow-up, nearly 47% of the depressed patients were loss to follow-up, mainly due to mortality (relative risk of 2.5 versus non-depressed comparisons) and cognitive impairment. Sixteen percent had an unfavorable course type, i.e. chronic or recurrent, 25% had a partial remission, and only 13% had a full remission. Nonetheless, almost half of those reaching full remission at six-year follow-up still had clinically relevant depression at two-year follow-up, which is an important finding and should encourage clinicians to prolong and optimize treatment in depressed older patients, even after two years.

We also demonstrated that results were biased in the direction of a more favorable prognosis if attrition was excluded as outcome, as this may lead to a selection of the more healthy and motivated patients (30% would have had an unfavorable course, 46% partial remission and 24% full remission). Furthermore, strict criteria were used to define full remission, as a result of which the proportion of patients with a full remission may be underestimated. The rationale for this decision was based on the previous finding that residual symptoms have been associated with a poor outcome,[48,49] indicating that the goal must be to keep the patient as symptom-free as possible.[48]

In a longitudinal study of 127 depressed older patients in the community, it was shown that at three years, 30% had died, 35% had a chronic or recurrent depression, 25% had another mental illness, and only 10% had maintained a full remission.[5] Stek et al. (2002) examined the long-term prognosis of major depression in hospitalized older patients six to eight year after clinical treatment and found that 40% had died, while among the survivors 33% had no residual symptoms or relapses,[11] which approximately corresponds to our finding that among survivors 24% reached full remission. These numbers from both community and clinical studies are in line with our results and strongly indicate that depression in later life is a disabling chronic disorder with a poor outcome.

Depression is a complex multifactorial disease, implicating that multiple factors from different domains of functioning contribute to its onset and prognosis.[21] This study found that an unfavorable course of depression was associated with a younger age of onset of depression, a higher severity of depression, chronic pain, neuroticism, and loneliness, which is in accordance with current literature.[4,26,28,50,51] Furthermore, partial remission could not be distinguished from full remission using depression-related clinical factors, but

was more likely associated with chronic diseases and loneliness. This finding could imply that these factors are important targets for interventions to prevent relapse, as partial remission is a strong predictor of relapse and chronicity.[52] Our findings do not point to single factors that may be important for the prognosis of depression, but rather point to multiple factors from different domains of functioning that all are important, with each factor having a small but significant contribution.

Recently, Brown et al. (2017) found that biological age was more important than chronological age in predicting the incidence and course of depressive symptoms over long-term follow-up.[53] The authors stated that their findings support the evolving biological view of late-life depression as resulting from deleterious age-associated changes.[53,54] Our study suggests however that a more holistic view allowing identification of non-biological factors as well, is appropriate in targeting older adults at risk for an unfavorable prognosis and thus for prevention and treatment interventions.[21,50]

Our study has some limitations. First, because of a lack of power, multivariate analyses were not performed on course types, making it difficult to clarify the strongest prognostic factors of an unfavorable course type. On the other hand, we did perform multivariate analyses using mixed models with the IDS as assessed every six months, which allowed a more accurate assessment of prognostic factors. Second, there might be a great chance of a Type I error due to multiple statistical comparisons. However, on a theoretical basis, we included multiple factors from biopsychosocial domains of functioning that have been previously associated with a poor outcome of late-life depression in studies to date, thereby minimizing the risk of Type I error (or chance). Also, most of the variables that remained statistically significant ($p<0.05$) in the final multivariate model, had a stronger association with the outcome in the preceding groupwise models at $p\leq0.01$ (except for 'age of onset'). Furthermore, predictors that were associated with a poor outcome from multinomial regression analyses, are more or less the same predictors that were associated with a poor outcome from mixed model analyses, which should affirm the validity of our findings. Moreover, the factors uncovered in this study are in line with previous research, from which we think that our results are solid and accurate. Third, although the strength of NESDO is that the results generalize to clinical practice, they are not generalizable to the community. Moreover, in the Netherlands general practitioners provide primary care for depression. Depressed patients who do not recover are subsequently referred to specialist mental health care. This situation may have induced some selection bias in our sample, with relatively many patients with a treatment-resistant depression. Finally, by using depression diagnosis at two measurement points over six years, information was lacking on short-term relapses and recurrences in between these measurements. Since recurrence and chronicity are

both unfavorable outcomes, this limitation was tackled by combining both groups. For future research, a latent class analysis on the IDS data would provide more detailed information about detailed trajectories of depression.

Despite of the limitations, the study has numerous strengths. The prognosis of late-life depression was captured based on the depression diagnosis according to DSM-criteria in combination with the IDS at separate measurement points over six years, which increases the external validity and usability for clinicians. Furthermore, we did not only examine the course, but also attrition among patients with late-life depression, which made it additionally clear that the long-term prognosis of late-life depression is poor.

The clinical implication of this study may be that a multidimensional approach targeting the uncovered factors is valuable in improving the prognosis of late-life depression. Depressed patients with a partial remission might benefit further from interventions targeting chronic diseases and loneliness to obtain full recovery. At the same time, the risk of a poor outcome, such as chronicity, cognitive impairment, or death may be inevitable in depressed patients when their depression is more severe, started at a younger age, and if health and psychosocial problems also exist. Careful long-term monitoring of depression among older adults may be key in optimizing maintenance treatment strategies.

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Supplemental

eTable 1. Characteristics of N=378 depressed patients at baseline, and according to their attrition status at follow-up

Determinants	Baseline Total N=378
Demographics	
Women, N (%)	250 (66.1)
Age, years, mean (SD)	70.7 (7.4)
Education, years, mean (SD)	10.4 (3.4)
Depression-related clinical factors	
Previous episode depression, yes, N (%)	17.2 (5.6)
Age of depression onset, mean (SD)	48.4 (20.6)
Severity depressive symptoms, mean (SD)	30.1 (13.0)
Comorbid anxiety diagnosis, yes, N (%)	147 (38.9)
Severity anxiety symptoms, mean (SD)	17.5 (11.4)
Global Cognitive Functioning, mean (SD)	27.7 (2.0)
Apathy, mean (SD)	17.2 (5.6)
Sleep problems, mean (SD)	10.6 (5.6)
Use of antidepressants, yes, N (%)	273 (72.8)
Frequent use of benzodiazepines, yes, N (%)	150 (39.7)
Health and lifestyle factors	
Chronic diseases, mean (SD)	2.1 (1.5)
Functional Limitations, mean (SD)	25.7 (12.4)
Metabolic syndrome, original ATP III criteria, yes, N (%)	127 (33.6)
Chronic Pain, yes, N (%)	210 (56.1)
Body-Mass-Index, mean (SD)	26.3 (4.4)
Physical activity, low, N (%)	114 (31.1)
Smoking, yes, N (%)	100 (26.7)
Alcohol, AUDIT, mean (SD)	2.6 (3.5)
Psychological and social factors	
Neuroticism, mean (SD)	39.1 (7.0)
Childhood Trauma Index, mean (SD)	1.0 (1.2)
Partner, no, N (%)	198 (52.4)
Loneliness, mean (SD)	6.6 (3.5)
Social support, poor, N (%)	177 (47.5)
Life events in past 5-year, mean (SD)	1.8 (1.3)

SD = standard deviation; IQR = interquartile range; AUDIT = Alcohol Use Disorders Identification Test
[a] For a statistical comparison of attrition (no/yes) at follow-up, χ^2 values have been computed for categorical variables and t-values for interval variables

	Attrition at six-year, i.e. loss to follow-up			
	No N=201	Yes N=177	Test Value[a] (df)	p-value
	137 (68.2)	113 (63.8)	X^2 = 0.78 (1)	.38
	69.0 (6.5)	72.8 (7.8)	t = 26.65 (1)	<.001
	10.9 (3.5)	9.9 (3.4)	t = 6.55 (1)	.011
	16.8 (5.3)	17.8 (5.8)	X^2 = 0.64 (1)	.09
	46.3 (19.7)	50.7 (21.5)	t = 4.24 (1)	.040
	29.7 (12.5)	30.6 (13.6)	t = 0.40 (1)	.53
	79 (39.3)	68 (38.4)	X^2 = 0.03 (1)	.86
	16.8 (10.7)	18.4 (12.2)	t = 1.72 (1)	.19
	28.1 (1.6)	27.2 (2.3)	t = 18.26 (1)	<.001
	16.8 (5.3)	17.8 (5.8)	t = 2.89 (1)	.09
	10.9 (5.2)	10.2 (5.9)	t = 1.20 (1)	.28
	145 (72.9)	128 (72.7)	X^2 = 0.00 (1)	.98
	73 (36.3)	77 (43.5)	X^2 = 2.03 (1)	.15
	2.1 (1.5)	2.2 (1.4)	t = 0.49 (1)	.49
	25.0 (12.3)	26.4 (12.4)	t = 1.11 (1)	.29
	61 (30.3)	66 (37.3)	X^2 = 2.03 (1)	.15
	111 (55.5)	99 (56.9)	X^2 = 0.07 (1)	.79
	26.1 (4.3)	26.6 (4.6)	t = 1.03 (1)	.31
	47 (24.1)	67 (39.0)	X^2 = 9.41 (1)	.002
	47 (23.4)	53 (30.5)	X^2 = 2.39 (1)	.12
	2.7 (3.5)	2.4 (3.4)	t = 0.75 (1)	.39
	39.1 (6.2)	38.9 (7.8)	t = 0.06 (1)	.80
	1.0 (1.2)	1.0 (1.2)	t = 0.01 (1)	.92
	106 (52.7)	92 (52.0)	X^2=0.02 (1)	.88
	6.6 (3.5)	6.7 (3.5)	t =0.05 (1)	.82
	96 (48.0)	81 (46.8)	X^2=0.05 (1)	.82
	1.8 (1.3)	1.7 (1.4)	t =0.47 (1)	.49

eTable 2. Determinants of six-year attrition in depressed patients (N=378) using Logistic Regression

	Bivariate OR (95% CI)	Multivariate OR (95% CI)
Demographics		
Women	0.83 (0.54-1.26)	
Age	**1.08 (1.05-1.11)**	**1.06 (1.03-1.09)**
Education	**0.93 (0.87-0.98)**	0.95 (0.88-1.01)
Depression-related clinical factors		
Previous episode depression	0.88 (0.45-1.72)	
Age of depression onset	**1.01 (1.00-1.02)**	1.00 (0.99-1.02)
Severity depressive symptoms (IDS)	1.01 (0.99-1.02)	
Comorbid anxiety diagnosis	0.96 (0.64-1.46)	
Severity anxiety symptoms (BAI)	1.01 (0.99-1.03)	
Global Cognitive Functioning (MMSE)	**0.79 (0.71-0.88)**	**0.85 (0.75-0.95)**
Apathy	1.03 (1.00-1.07)	
Sleep problems	0.98 (0.94-1.02)	
Use of antidepressants	0.99 (0.63-1.57)	
Use of benzodiazepines	1.35 (0.89-2.04)	
Health and lifestyle factors		
Chronic diseases	1.05 (0.92-1.20)	
Functional Limitations	1.01 (0.99-1.03)	
Metabolic syndrome, yes	1.37 (0.89-2.09)	
Chronic Pain	1.06 (0.70-1.59)	
Body-Mass-Index	1.02 (0.98-1.07)	
Physical Activity, low	**2.01 (1.28-3.15)**	1.38 (0.85-2.25)
Smoking, yes	1.44 (0.91-2.27)	
Alcohol use	0.97 (0.92-1.03)	
Psychological and social factors		
Neuroticism	1.00 (0.97-1.03)	
Childhood Trauma Index	0.99 (0.84-1.17)	
Partner, no	0.97 (0.65-1.45)	
Loneliness	1.01 (0.95-1.07)	
Social support, poor	0.95 (0.64-1.43)	
Life events	0.95 (0.82-1.10)	

OR = odds ratio; bold indicates statistically significant based on the 95% confidence interval (CI) with $p<0.05$

Chapter 7

Summary and general discussion

7.1 Introduction

The general aim of this thesis was to investigate both time-trends in rates and excess mortality of depression, and the long-term outcome of depression in later life. The current chapter first summarizes the findings of the previous empirical chapters. Then methodological considerations will be discussed. Successively, implications for public health and clinicians, i.e. physicians, will be considered. The chapter will end discussing recommendations for future research.

7.2 Summary of Findings

The first aim (***chapter 2***) was to investigate secular trends in the exposure to risk and protective factors of depression and whether these trends are associated with secular trends in the prevalence of depression. Three birth cohorts of 55-64-year-olds from the population-based Longitudinal Aging Study Amsterdam were examined on depression prevalence using identical methods in 1992 (n=944), 2002 (n=964) and 2012 (n=957). A two-stage screening design was used to identify subthreshold depression (SUBD) and major depressive disorder (MDD). We found that compared with 1992, MDD became more prevalent in 2002 (OR: 1.90, 95%-CI: 1.10-3.28, p=0.022) and 2012 (OR: 1.80, 95%-CI: 1.03-3.14, p=0.039). This was largely attributable to an increase in the prevalence of chronic diseases and functional limitations. Socioeconomic and psychosocial improvements, including an increase in labor market participation, social support and mastery, hampered MDD-rates to rise more and were also associated with a 32% decline of SUBD-rates in 2012 as compared to 2002 (OR: 0.68, 95% CI: 0.48-0.96, p=0.03). We concluded that among late middle-aged adults, there is a substantial net increase of MDD, which is associated with deteriorating physical health. If morbidity and disability continue to increase, a further expansion of MDD-rates may be expected. However, improving socioeconomic and psychosocial conditions may benefit public health, as these factors were protective against a higher prevalence of both MDD and SUBD.

The second aim (***chapter 3***) was to investigate birth-cohort differences in the incidence of depression and their explanatory factors. A cohort difference in depression incidence (score ≥ 16 on the Center for Epidemiological Depression scale) was examined by comparing two identically measured cohorts of non-depressed 55-64-year olds, 10-years apart, with nine-years follow-up. Baseline measurements took place in 1992/93 (early cohort, n=794), and 2002/03 (recent cohort, n=771). According to the dynamic equilibrium model of depression, potential explanatory factors were distinguished in risk and protective factors. We found a 29% risk reduction in incident depression in the recent cohort, which was primarily related to an increase in protective factors, including an increase in education, mastery and labor market participation. If risk factors, including chronic diseases and functional limitations, had not increased the incidence would have declined further. We concluded that protective factors counterbalanced risk factors in declining depression incidence rates. However, maintaining a good physical health must be a priority to further decrease depression rates.

The third aim (***chapter 4***) was to investigate secular trends in excess mortality of late-life depression and, if a secular trend was present, to investigate gender differences in the trend, and to find explanatory factors for the trend. We examined secular trends in

excess mortality of depression by using a cohort-sequential-longitudinal study of 4,084 community-dwelling older adults in the Netherlands based on data from the Longitudinal Aging Study Amsterdam (LASA). Six measurement cycles were included from 1992/93 until 2008/09, each linked to the overall 5-year mortality, covering a 16-year time span. We found a downward trend in excess mortality of MDD, adjusted for age and gender, which could not be explained by education, health and lifestyle factors, nor antidepressants use. Gender differences in the trend were not found. No trend in excess mortality of SUBD was found. We concluded a favorable development in excess mortality of community-dwelling older adults with MDD, while those with SUBD did not show a clear trend in excess mortality.

The fourth aim (***chapter 5***) was to investigate a wide range of vulnerability and stress related variables in a longitudinal design with up to 17-years of follow-up to identify both predictors of MDD and recovery in a population-based sample of older people with SUBD. We examined N=341 eligible participants with SUBD from the Longitudinal Aging Study Amsterdam (LASA) over a 17-year observational period. We found that N=153 (44.9%) recovered from SUBD, N=138 (40.5%) remained chronically SUBD, and N=50 (14.7%) developed MDD. Women, high neuroticism, more chronic diseases, high body-mass-index, smoking and less social support predicted conversion to MDD. Men, low neuroticism and absence of pain predicted recovery from SUBD. We concluded that although older people with SUBD are clearly at risk of developing MDD, the majority did not, even after a long and thorough follow-up. Given the risk factors that were uncovered, targeting and prevention of MDD in those at very high risk is feasible.

The fifth aim (***chapter 6***) was to examine the long-term prognosis of late-life depression, in terms of both main reasons for attrition and course types, in clinically depressed patients over six-years. We examined the six-year prognosis of 378 patients with late-life depression and identified prognostic factors of an unfavorable course, using data from The Netherlands Study of Depression in Older persons (NESDO). We found that at six-year follow-up, 46.8% had dropped out, 15.9% had an unfavorable course, i.e. chronic or recurrent, 24.6% had partial remission, and 12.7% had full remission. The relative risk (RR) of mortality in depressed patients was 2.5 when compared with non-depressed comparisons. An unfavorable course of depression was associated with a younger age of depression onset, higher symptom severity of depression, pain, neuroticism, and loneliness at baseline. Additionally, partial remission was associated with chronic diseases, and loneliness at baseline when compared with full remission. We concluded that the long-term prognosis of late-life depression is poor, with regard to mortality and course of depression. Chronic diseases, loneliness, and pain may be used as putative targets for optimizing prevention and treatment strategies of relapse and chronicity.

7.3 Methodological Considerations

Strengths

Community-based epidemiological studies are able to provide data on the natural history of a disorder, including risk and protective factors, prodromal states, onset of illness, and disease progression. LASA is a representative ongoing prospective cohort study on the older adult population in the Netherlands since 1992, whereas NESDO is a multi-site naturalistic cohort study including a relatively large and unique sample of clinically depressed patients, which is the major strength of NESDO. In addition to LASA, NESDO offers the opportunity to examine the determinants, long-term course and consequences of depressive disorders in more detail.

A major strength of LASA is its rigorous design with a long-term follow-up. LASA is primed to examine cohort differences in a reliable and valid manner by using identical measurements across cohorts, including a two-stage screening design to identify cases of SUBD and cases with MDD. The relatively rich collection of risk and protective factors of depression in LASA has enabled systematically testing the effects of putative risk and protective explanatory factors on the occurrence of depression over time, which is unique and innovative to our knowledge. Furthermore, the approach to include SUBD in our studies is important, because evidence has been growing that SUBD is also a crucial determinant of public health and a major risk factor for MDD.[1,2] Finally, essential information has been gathered concerning secular trends in risk and protective factors for depression, which can be used in future research.

Limitations

In general, the potential of selection bias has to be considered in cohort studies as these, as participants of community-based (and even more in clinical-based) studies are often the most motivated and healthy individuals. Thus, depressed individuals may less likely participate than non-depressed individuals, which may result in an underestimation of depression rates. Also, loss to attrition may have underestimated the findings from our long-term outcome studies, because it is well known that depression is associated with excess mortality. Therefore, in our NESDO study, the rate and reason of attrition was separately addressed to be able to draw a more complete picture of the long-term course of depression. Because of the three-yearly follow-up in LASA, the incidence rate of depressed cases may be underestimated since the occurrence of depression between follow-up measurements could have been missed. Moreover, participants were asked whether an episode of MDD occurred in the past year, which may hold the risk of recall bias. However, these limitations are not likely to have affected the cohort comparisons, because each cohort had the same follow-up schedule.

With regard to our study on excess mortality of depression, results should be interpreted with caution, because studies investigating trends in excess mortality of late-life depression are scarce and should be replicated. Our findings on time-trends in rates and excess mortality of depression do not imply trends in other countries. Furthermore, LASA lacked information on specific causes of death, such as cardiac death or suicide, having this information could improve the specificity of the findings. Another important limitation of the LASA study was the sample size regarding those having depression, which may have adversely affected the power of some analyses. In particular the number of MDD events were small, relative to the number of predictor variables we wanted to analyze, which hold the risk of Type-I and/or Type-II errors.

In NESDO there was also a lack of power regarding the multivariate analyses on the course types, making it difficult to clarify the strongest prognostic factors of an unfavorable course type. On the other hand, we did perform multivariate analyses using mixed models with the IDS as assessed every six months, which allowed a more accurate assessment of prognostic factors. Also, this method corrects the problem of inflated risk of Type I errors resulting from numerous statistic tests performed by bivariate multinomial regression. Furthermore, by using the depression diagnosis at two measurement points over six years, information was lacking on short-term relapses and recurrences in between these measurements. However, since recurrence and chronicity are both unfavorable outcomes, this limitation was tackled by combining both groups.

7.4 Implications

Public Health

The Netherlands population is aging more and more rapidly. According to Statistics Netherlands (CBS) estimates the proportion of the Netherlands population over the age of 65 will rise from 16.8% in 2000 (2.6 million) to 31.4% (5.0 million) in 2030. From these numbers, the need has become clear that the occurrence of depression in later life (with mean prevalence rates of 10% and 2.5% for subthreshold depression and major depressive disorder respectively) has to be prevented.

Since secular trends in the prevalence and incidence of depression were found among late middle-aged adults that were influenced by a dynamic equilibrium of more or less modifiable risk and protective factors, the most important public health message drawn from this thesis is that depression rates in the community can be prevented. In addition, the second important message deriving from our findings is not only the possibility, but also the importance to prevent depression in an early stage, because we found that the long-term outcome of depression in later life is poor. Accordingly, the statement "prevention is better than cure" may be obvious for depression in later life.

The finding that educational level, labor market participation, mastery and network size had increased in more recent cohorts has been supported by others and indicate that socioeconomic and psychosocial circumstances have improved for more recent generations,[3–5] which enhance protection against depression. The finding that an increased use of antidepressants in 2002 and 2012 as compared to 1992 had an additional explanatory effect on the secular trends found in MDD prevalence may be the consequence of an improved recognition and treatment of MDD.[6–8] Furthermore, the finding that excess mortality of MDD in later life had declined in recent decades may also suggest that prevention strategies and improved treatments of MDD provide a return on the investment in recent decades, which may be appreciated by policy makers and caregivers. Nevertheless, assuming that MDD prevalence will further increase, despite improvement in psychiatric treatment, socioeconomic and psychosocial circumstances, we can expect a continued increase in burden of disease that will challenge the field of mental and public health.

Lessons may be learned from somatic medicine, for example, as cardiovascular disease (CVD) has become less prevalent in recent decades through a lower exposure to CVD risk factors, such as hypercholesterolemia, smoking, and high blood pressure.[9] Extensive literature is available documenting the effects of different strategies to prevent major depressive disorder.[10] These focus on (a) the whole population (universal prevention),

(b) those at risk due to exposure to known risk factors for MDD (selective prevention) and (c) those at even higher risk of MDD due to their exhibiting prodromal signs and symptoms of depression (indicated prevention). Several studies among all age groups have demonstrated that selective and indicated prevention of depression is feasible, effective and cost-effective.[11–13] Indicated prevention is delivered using low cost psychological interventions and may reduce the incidence of MDD at six months by 39%, yielding a number needed to treat (NNT) that was estimated at 10.[14] This compares favorably with preventative interventions elsewhere in medicine. For example, the NNT with any statin to prevent one case of cardiovascular disease over five years was estimated 33 and 37 respectively for men and women.[15]

Clinical

In general, clinicians should obtain a holistic view in their approach to recognize and treat depression along its continuum. They must recognize that not only major depressive disorder, but also milder depression, is a devastating long-lasting condition associated with poor health outcomes. Psychiatrists, psychologists, and other mental health workers should prioritize preventive interventions, and seek or define their collaboration with general practitioners, who are often the first to examine patients with mild depressive symptoms. Interviewing patients according to the biopsychosocial matrix, and distinguish risk factors from protective factors may help in choosing the appropriate prevention or treatment strategy. Not only focusing on diminishing the risk factors, but also strengthening the protective factors may better equip clinicians in their aid to treat patients with depression.

Specific to the older adult population, depression often goes unrecognized and untreated, because many people may think that depression is a normal part of aging, i.e. a natural reaction to a comorbid chronic disease, disability, loss, social transition and loneliness. However, depression in later life subsequently increases the risk of developing other medical diseases, cognitive decline, and dementia. Moreover, unrecognized and untreated depression in later life has fatal consequences in terms of both suicide and non-suicide mortality.

We found that the majority of people with late-life SUBD spontaneously recovers, therefore 'watchful waiting' seems adequate in this group, especially in men and people with low neuroticism. Clinicians might also pay attention to pain and its management, as our results suggest that pain may be an obstacle to recover from SUBD. People with SUBD that are at (very) high risk of conversion to MDD may be selected for indicated prevention programs, including low cost psychological interventions.[16] Furthermore, clinicians should focus their treatments on the adequate management of comorbid chronic diseases,

influence bad lifestyle behaviors - stop smoking and increase physical activity to reduce weight - and improve social support if necessary. These recommendations has also been reported by others.[17]

Patients with a major depressive disorder that reach a partial remission might benefit further from interventions targeting chronic diseases and loneliness. At the same time, depressed patients with severe depression, health problems including somatic co-morbidity and pain, and psychosocial problems are at high risk of chronicity and poor outcome, including cognitive impairment,[18] and premature mortality.[19] Careful long-term monitoring of depression among older adults may be key in optimizing maintenance treatment strategies. Like diabetes or arthritis, depression among older adults should be viewed as a chronic disease. Getting well is only the beginning of the challenge, the goal is staying well.

7.5 Future Research

The study of secular trends in mental health is a matter of ongoing importance. Our current understanding about time trends in the occurrence of depression is still not completely understood. This thesis has made an important contribution to the literature in two ways, first because it was demonstrated that depression rates are not stable across generations, and second because factors were identified that explained the shifts found in depression rates. Future research should investigate whether the same trends can be found and explained in other age groups, and in other countries. Furthermore, also cohort differences in the course of depression (i.e. duration) have to be investigated, because the duration together with the incidence of depression determines the prevalence, and thus the burden of disease. More detailed insight into the epidemiology of depression, including information on time trends, will help the field to move forward in the global priority to reduce the disease burden of depression.[20]

The next step would be to translate our epidemiological findings into a (clinical) research program that aims to reduce depression rates in later life, as well as to improve the long-term prognosis of late-life depression. However, this is a rather complicated challenge, since depression is a multifactorial disease with each factor having a small contributing effect. Because somatic diseases does seem to play a dominant role in the etiology and prognosis of depression, another approach may be to study whether and how somatic diseases influence depression rates and vice versa. For example, at the population level, it can be studied whether the available prevention programs for somatic diseases (and dementia), which collectively promote healthy lifestyles (i.e. healthy diet, no smoking, no alcohol, and stimulate physical activity), also influence depression rates and to what extent. Also, an increasing number of initiatives have been available in recent years that target loneliness and social isolation among community-dwelling older adults. It would be interesting to study whether these initiatives also will reduce depression rates in later life, since a bidirectional relationship has been assumed between loneliness and (mild) depression. Finally, clinical studies may be initiated, with the psychiatrist more closely collaborating with the somatic specialist, i.e. cardiologist, internist, and neurologist, to setup and study selective and indicated prevention programs for depression in somatically compromised patients.

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Appendix

Nederlandstalige samenvatting

Inleiding

Depressie gaat gepaard met een enorme ziektelast, zowel voor de patiënt als voor de gemeenschap, ongeacht de leeftijd. Depressie bij ouderen is geassocieerd met negatieve gezondheidsuitkomsten, zoals een hogere zorgconsumptie, vermindering van kwaliteit van leven, functionele beperkingen, dementie en zelfs voortijdig overlijden. Er wordt geschat dat 10-15% van de ouderen een depressie heeft, waarvan een kwart een ernstige depressie (MDD, major depressive disorder) en de rest een beperkte depressie (SUBD, subthreshold depression). Bij een beperkte depressie is er sprake van klinisch relevante depressieve klachten, die niet ernstig genoeg zijn om een depressie diagnose te stellen. De vraag of depressie tegenwoordig vaker voorkomt dan vroeger is een terugkerend en enigszins controversieel thema, echter is nog niet goed onderzocht. Hoewel er verschillende studies bestaan die het aantal mensen met een depressie over de tijd hebben vergeleken, zogenoemde time-trends, zijn er geen studies geweest die daarbij ook de risicofactoren en beschermende factoren van een depressie hebben meegenomen. Het percentage mensen dat een bepaalde ziekte krijgt wordt meestal uitgedrukt in prevalentie en incidentie. Prevalentie betreft de *bestaande* ziektegevallen in een populatie binnen een bepaalde tijd en incidentie betreft de *nieuwe* ziektegevallen in een populatie binnen een bepaalde tijd. Het ontstaan van depressie heeft niet één aanwijsbare oorzaak, maar wordt door veel verschillende factoren bepaald. Het dynamisch evenwichtsmodel van depressie veronderstelt dat er een balans bestaat tussen vele risicofactoren enerzijds en vele beschermende factoren anderzijds. Bij een disbalans kan een depressie ontstaan. Enkele voorbeelden van risicofactoren zijn lichamelijke ziekte, neuroticisme (persoonlijkheidseigenschap dat zich kenmerkt door een neiging tot emotionele instabiliteit) en eenzaamheid. Enkele voorbeelden van beschermende factoren zijn hoog opleidingsniveau, hoog niveau van mastery (persoonlijkheidseigenschap dat zich kenmerkt door een groot gevoel van regie te ervaren over het eigen leven), en goede sociale steun. Het eerste gedeelte van het proefschrift behelst onderzoek naar de vraag of time-trends in risico en beschermende factoren voor depressie geassocieerd zijn met time-trends in de prevalentie en incidentie van depressie. Omdat depressie sterk samenhangt met voortijdig overlijden, worden bovendien time-trends onderzocht in depressie-gerelateerde sterfte. In het tweede gedeelte van het proefschrift wordt in meer detail onderzocht hoe het lange termijn beloop van depressie bij ouderen eruitziet. Deze resultaten zijn van belang omdat meer kennis over factoren die interfereren met een gunstig beloop van depressie gebruikt kunnen worden voor het ontwikkelen van preventieprogramma's om het aantal mensen met een depressie (prevalentie en incidentie) en de daarmee gepaard gaande ziektelast terug te dringen.

Het belang van het bestuderen van time-trends in de geneeskunde kan worden geïllustreerd aan de hand van twee veelvoorkomende ziektebeelden die beide, net als depressie, gepaard gaan met een enorme ziektelast, te weten hart- en vaatziekte en diabetes mellitus. Uit onderzoek blijkt dat het aantal mensen met een hart- en vaatziekte over de tijd afneemt. Deze daling wordt verklaard doordat een aantal belangrijke risicofactoren voor hart- en vaatziekte over de tijd is afgenomen (zoals roken, hypercholesterolemie en verhoogde bloeddruk). Tegelijkertijd is het aantal mensen met diabetes mellitus over de tijd toegenomen. Deze toename wordt verklaard doordat een aantal risicofactoren voor die ziekte, zoals overgewicht of obesitas en sedentair gedrag (overmatig zitten), is toegenomen. Door te onderzoeken of time-trends in risicofactoren van een ziekte geassocieerd zijn met time-trends in het percentage mensen dat die ziekte krijgt kunnen belangrijke factoren worden opgespoord die vervolgens gebruikt kunnen worden voor het ontwikkelen van preventieprogramma's. Zo heeft een beter cardiovasculair risicomanagement bijgedragen aan een gedaald aantal mensen met een hart- en vaatziekte.

Met behulp van data uit de Longitudinal Aging Study Amsterdam (LASA) en de Netherlands Study of Depression in Older persons (NESDO) worden de volgende vragen in het proefschrift beantwoord: 1) Zijn er in 2012 meer 55-64-jarigen met een depressie dan in 2002, respectievelijk 1992 (time-trends in prevalentie)? Zo ja, kan dit verklaard worden door een veranderde blootstelling aan risico- en beschermende factoren? 2) Zijn er verschillen tussen 1992 en 2002 in het aantal ouderen dat een depressie ontwikkelt over negen jaar tijd (time-trends in incidentie)? Zo ja, kan dit worden verklaard? 3) Verandert de sterfte over de tijd bij ouderen met een depressie in de algemene bevolking? Zo ja, kan dit worden verklaard? 4) Wat is het lange termijn beloop van de beperkte depressie (SUBD) en wat zijn voorspellers van een ernstige depressie (MDD) en voorspellers van herstel? 5) Wat is de lange termijn prognose van depressieve oudere patiënten, meer specifiek in termen van uitval uit de studie en beloop van depressie?

Resultaten

In **hoofdstuk twee** werd de associatie onderzocht tussen time-trends in de prevalentie van depressie en time-trends in de blootstelling aan risicofactoren en beschermende factoren voor depressie. Daartoe werden drie geboortecohorten van 55-64-jarigen uit de Nederlandse bevolking met elkaar vergeleken in 1992 (n=944), 2002 (n=964) en 2012 (n=957). Hierbij werd gebruik gemaakt van identieke meetinstrumenten. Depressie werd geïdentificeerd met een tweetrapsscreening waarin de beperkte depressie (SUBD) en ernstige depressie (MDD) werden onderscheiden. We zagen dat zowel in 2012 als in 2002, de ernstige depressie bijna twee keer zo vaak voor kwam dan in 1992. Deze stijging was grotendeels geassocieerd met een toegenomen prevalentie van chronische ziektes en functionele beperkingen. Verbeterde sociaaleconomische en psychosociale omstandigheden (zoals arbeidsmarktparticipatie, opleidingsniveau, sociale steun en mastery) beschermde tegen een grotere toename van ernstige depressie en verklaarde ook de gevonden daling (32%) in de prevalentie van een beperkte depressie in 2012 vergeleken met 2002. We concludeerden dat het aantal mensen met een ernstige depressie aanzienlijk was toegenomen in de twee recentere cohorten, wat gepaard ging met een verslechtering van de algehele lichamelijke gezondheid in diezelfde cohorten. We verwachten dat wanneer de lichamelijke gezondheid in de algemene samenleving verder zal verslechteren, dit gepaard zal gaan met een toenemend aantal mensen met een ernstige depressie. Echter, investeren in verbetering van psychosociale en sociaaleconomische omstandigheden kan de volksgezondheid ten goede komen, omdat deze factoren zowel beschermend bleken tegen een hogere prevalentie van een ernstige depressie als een beperkte depressie.

In **hoofdstuk drie** werd een time-trend in depressie-incidentie onderzocht (aantal niet-depressieve mensen dat een depressie ontwikkelt na follow-up) door twee identiek gemeten geboortecohorten van niet-depressieve 55-64-jarigen met elkaar te vergelijken met beide een follow-up van negen jaar. Baseline metingen vonden plaats in 1992 (vroege cohort, n = 794), en 2002 (recente cohort, n = 771). Volgens het dynamische evenwichtsmodel van depressie werden mogelijk verklarende factoren onderscheiden in risico- en beschermende factoren. We vonden een risicoreductie van 29% voor depressie-incidentie in het recente cohort, hetgeen gedeeltelijk verklaard werd door een toename van beschermende factoren (zoals opleidingsniveau, arbeidsmarktparticipatie en mastery). Als risicofactoren, waaronder chronische ziektes en functionele beperkingen, niet waren toegenomen dan zou de incidentie van depressie verder zijn afgenomen. Uit dit onderzoek werd geconcludeerd dat een gunstige ontwikkeling van beschermende factoren, een ongunstige ontwikkeling van risicofactoren voor depressie hebben gedomineerd waardoor de incidentie van depressie is gedaald. Echter, bevorderen van een goede lichamelijke gezondheid moet een prioriteit zijn om het aantal mensen met een depressie in de toekomst verder te verlagen.

In **hoofdstuk vier** werd onderzocht of er time-trends bestaan in sterfte bij ouderen met een depressie en, indien aanwezig, om te onderzoeken of dit voor mannen en vrouwen gelijk was en welke verklarende factoren gevonden konden worden. Daartoe werd gebruik gemaakt van 4.084 thuiswonende ouderen uit de Nederlandse LASA-studie. De studie bestond uit zes meetmomenten vanaf 1992/93 tot 2008/09 (algehele periode van 16 jaar), waarbij elk meetmoment gekoppeld was aan de totale sterfte binnen 5-jaar. We observeerden dat de sterfte bij ouderen met een ernstige depressie afnam over de tijd, ook gecorrigeerd voor leeftijd en geslacht, hetgeen niet verklaard kon worden door factoren als opleidingsniveau, lichamelijke gezondheid, levensstijl, noch door gebruik van antidepressiva. Er werd geen verschil gevonden tussen mannen of vrouwen. Bij ouderen met een beperkte depressie werd echter geen trend gevonden in de sterfte. Kortom, een afname werd gevonden van de sterfte bij ouderen met een ernstige depressie, terwijl ouderen met een beperkte depressie geen duidelijke afname in sterfte lieten zien.

In **hoofdstuk vijf** werden voorspellers onderzocht van een ernstige depressie als ook van herstel bij ouderen met een beperkte depressie in de Nederlandse samenleving die langdurig (maximaal 17 jaar) zijn gevolgd. 341 ouderen met een beperkte depressie werden uit de LASA-studie geïncludeerd. We vonden dat 153 (44,9%) mensen herstelden van een beperkte depressie, 138 (40,5%) mensen bleven chronisch beperkt depressief en 50 (14,7%) mensen ontwikkelden een ernstige depressie. Het risico op overgang van een beperkte naar een ernstige depressie werd verhoogd door het vrouwelijke geslacht, hoog neuroticisme, chronische ziektes, hoge body-mass-index (BMI), roken en beperkte sociale steun. De kans op herstel van een beperkte depressie naar niet-depressief werd verhoogd door het mannelijke geslacht, laag neuroticisme en afwezigheid van pijn. We concludeerden dat hoewel ouderen met een beperkte depressie duidelijk een verhoogd risico lopen op het ontwikkelen van een ernstige depressie, de meerderheid dit niet kreeg. Gegeven de risicofactoren die werden ontdekt, zou het richten en voorkomen van een ernstige depressie bij ouderen met een zeer hoog risico haalbaar kunnen zijn.

In **hoofdstuk zes** werd de langetermijnprognose van depressie bij 378 depressieve patiënten onderzocht, zowel wat betreft de belangrijkste redenen voor uitval uit de studie als ook het beloop van depressie. Daartoe werd gebruik gemaakt van gegevens uit de NESDO-studie. Na zes jaar follow-up deed 46,8% van de oorspronkelijke deelnemers niet meer mee aan de studie. Van de 53,2% van de deelnemers die nog wel meededen had 15,9% een ongunstig beloop (chronisch of recidiverend), 24,6% een gedeeltelijke remissie en 12,7% een volledige remissie. Het risico op overlijden bij depressieve patiënten was 2,5 keer hoger dan in niet-depressieve personen. Een ongunstig beloop van depressie was geassocieerd met een jongere leeftijd waarop de depressie begon, een hogere ernst van de symptomen van depressie, pijn, neuroticisme en eenzaamheid bij aanvang van de studie.

Bovendien hadden depressieve ouderen met een gedeeltelijke remissie vaker chronische ziektes en meer eenzaamheid in vergelijking met ouderen die volledige herstelden van hun depressie. We concludeerden dat de langetermijnprognose van depressie bij ouderen ongunstig is, zowel met betrekking tot sterfte als ook het beloop van de depressie. Chronische ziekte, eenzaamheid en pijn kunnen worden gebruikt als speerpunten voor interventie in mogelijke toekomstige preventie- en behandelingsstrategieën van terugval en chroniciteit.

Conclusie

De Nederlandse bevolking vergrijst steeds sneller. Naar schatting van het Centraal Bureau voor de Statistiek zal het aandeel van de Nederlandse bevolking boven de 65 jaar stijgen van 16,8% in 2000 (2,6 miljoen) tot 31,4% (5,0 miljoen) in 2030. Uitgaande van een gemiddeld prevalentiepercentage van 10%-15%, betekent dit dat er in 2030 rond de 500.000 tot 750.000 ouderen met een depressie zullen zijn. Gegeven de enorme ziektelast die met depressie gepaard gaat, lijkt preventie van depressie daarom noodzakelijk en dit zou hoog op de agenda moeten staan. Mijn onderzoek laat zien dat er time-trends bestaan in de prevalentie en incidentie van depressie, welke gedeeltelijk verklaard kunnen worden door een dynamisch evenwichtsmodel van min of meer te beïnvloeden risico- en beschermende factoren, zoals chronische ziektes, functionele beperkingen, pijn, overgewicht, neuroticisme en eenzaamheid respectievelijk opleidingsniveau, arbeidsmarktparticipatie, mastery en sociale steun. De belangrijkste boodschap die hieruit voortvloeit is dat het aantal mensen met een depressie over de tijd verre van stabiel is en dus beïnvloedbaar lijkt. Bovendien laten de resultaten aangaande het ongunstige beloop van depressie bij ouderen op de langere termijn zien dat het extra van belang is om depressie in een vroeg stadium te herkennen en (erger) te voorkomen. Het adagium “voorkomen is beter dan genezen” is voor depressie op latere leeftijd dan ook zeer terecht.

Appendix

Dankwoord

Dankwoord

Velen hebben, direct of indirect, bijgedragen aan de totstandkoming van dit proefschrift. Een aantal daarvan wil ik hier graag vermelden.

Om te beginnen wil ik mijn opleider en voorzitter van de leescommissie Ton van Balkom bedanken. Beste Ton, aan jou heb ik veel te danken wat betreft mijn (beginnende) loopbaan in de psychiatrie. Na de geneeskundeopleiding wilde ik graag voor de opleiding psychiatrie naar de grote stad, Amsterdam. Willem Nolen, destijds mijn stagebegeleider wetenschap in het UMCG, wees mij op jouw naam. Hij roemde de brede opleiding bij GGZ inGeest-VUmc, waarin zowel ruim aandacht was voor perifere als academische werkzaamheden. Die keuze bleek algauw een schot in de roos. Geïnspireerd door collegae die hun AIOS-opleiding combineerden met onderzoek, schreef ik op een beschikbare vacature voor een promotietraject in de ouderenpsychiatrie. Enigszins verrast was je wel dat ik schreef, maar niet minder enthousiast. Het sollicitatiegesprek met de promotiecommissie was snel geregeld! Ton, bedankt voor de verdieping en steun tijdens onze mentorgesprekken, de gezelligheid en gastvrijheid op informele bijeenkomsten, zoals dansen op de Corsendonkcursus of gewoon lekker eten met collega's bij jou thuis.

Beste Aartjan, onze eerste kennismaking was vrij formeel, tijdens mijn sollicitatiegesprek waarin je meermaals vroeg naar mijn interne motivatie om onderzoek te willen doen. Die vraag prikkelde mij en ik wist geen goed antwoord te geven. Even was ik bang dat ik daardoor geen geschikte kandidaat was. Gelukkig kreeg ik toch de kans. Pas enkele jaren geleden tijdens een APH-research meeting wist ik wat ik had moeten antwoorden: op de vraag aan de zaal wie onderzoek doet om zijn/haar beroemdheid te vergroten, zag ik jouw hand, en die van Brenda, gretig de lucht ingaan. ;) Jouw inzicht in theoretische onderbouwingen bij het opstarten van onderzoek werkt inspirerend, ook de integriteit waarmee je onderzoek bedrijft en begeleid. Daarnaast het gemak waarmee jij een tekst reviseerde tot een sluitend geheel heb ik als een enorme kracht beschouwd. Aartjan, ontzettend bedankt voor de kans die je me hebt gegeven en jouw onmisbare rol in het geheel, als wetenschappelijk leermeester ben ik je zeer erkentelijk.

Beste Max, voordat het onderzoek begon hadden wij reeds een voorzichtige kennismaking gehad via Caroline, vanwege mijn wens om ouderenpsychiater te willen worden. Ik heb jou als een heel enthousiast persoon ervaren, zowel in de kliniek als in de begeleiding van mijn onderzoek. Zeker wanneer ik weer met nieuwe onderzoeksresultaten aankwam, vond je dit mooi, je complimenteerde me dan met de gedane analyses waardoor mijn

zelfvertrouwen groeide. Buiten het werk om, stonden we vaak ook even stil bij elkaars privéleven, die momenten koester ik en laten ook zien dat er meer is dan werk alleen. Max, dank voor je begeleiding, betrokkenheid en de wijze lessen!

Beste Martijn, als nieuw aangestelde directeur van LASA kreeg je mij in de schoot geworpen met de vraag om copromotor te zijn. Dat heb je geweten, denk ik, zeker in het begin toen je me aan de hand nam en stap voor stap moest voordoen hoe een syntax te bouwen in SPSS. Gaandeweg is de praktische ondersteuning meer omgezet in een inzichtelijke ondersteuning. Jouw scherpte, vanuit een andere (niet-klinische) invalshoek, was een onmisbare schakel in het geheel, dank hiervoor. Daarnaast ben ik zeer dankbaar voor de mogelijkheid die ik heb (gehad) om onderzoek te doen op het LASA-honk, omringd door inspirerende collega's binnen een geweldig leuk team. De goede infrastructuur van LASA, zowel qua data als werkomgeving, heeft zeker bijgedragen aan de succesvolle afronding van mijn proefschrift.

Beste Hannie, 'focus!' hoor ik jou nog zeggen. Vanuit de Oldenaller bij GGZ inGeest, na een kleine werkbespreking, keerde ik terug naar LASA met een A4 waarop enkel en alleen mijn onderzoeksvraag stond geschreven, die ik vervolgens van jou aan de muur moest hangen bij mijn computer (tot hilariteit van mijn collega-onderzoekers). Hannie, wat heb ik toch een heerlijke tijd gehad met jou aan mijn zijde tijdens het onderzoek. Jij was kortdaad, directief en structureerde mij enorm in het werk. Ook buiten het werk om was je een ware sparringpartner en een lief mens. Je hielp mij om te groeien in mijn rol als promovendus en om mijn mannetje te staan als mijn promotoren het artikel bijvoorbeeld 180 graden wilden draaien. Hannie, dank voor de bijzondere momenten.

Beste Dorly, vrij snel raakte je betrokken bij mijn promotieonderzoek als coauteur van meerdere papers, je hebt daardoor aanzienlijk bijgedragen aan de vorming van dit geheel. Jouw interesse in cohortverschillen werkte aanstekelijk, ik vond dit dan ook het meest spannende onderdeel van mijn proefschrift. Hoewel het een ontzettende opgave was om de verschillende datasets in elkaar te knopen en de analyses juist te interpreteren, heb ik ervan genoten om hierin samen met jou op te trekken en van jou te kunnen leren. Hartelijk dank Dorly voor de tijd die je, ongeacht jouw overvolle agenda, ruim maakte om mij te helpen.

Beste Emiel, op advies van Aartjan heb ik jou gaandeweg gevraagd c.q. betrokken bij meerdere LASA-papers en niet zonder spijt. Wat werd het onderzoek doen ineens een stuk leuker, om laagdrempeliger mijn enthousiasme te kunnen delen met een 'peer' en om van jou te leren 'right on the spot'. Jouw vernuftig stukje techniek om reviewers te selecteren kwam goed van pas toen een van onze papers ontelbare keren was afgewezen, prachtig.

Daarnaast genoot ik van je anekdotes uit de wetenschappelijke wereld en de geruchten over Ajax die je via jouw zus ontving. Dat we uit hetzelfde geboortecohort stammen (1984) en beiden een BBN-er hebben als zus (Bijna Bekende Nederlander) zal mogelijk hebben bijdragen aan de klik die ik met jou ervaar. Hopelijk blijven we in de toekomst met elkaar schrijven, papers bedoel ik.

Graag wil ik ook de leden van de leescommissie, professor Ton van Balkom, professor Richard Oude Voshaar, doctor Didi Rhebergen, professor Monique Verschuren, professor Karien Stronks, professor Brenda Penninx en professor Pim Cuijpers, hartelijk danken voor het kritisch beoordelen van het manuscript.

Beste Wouter en Maarten, mijn paranimfen, wat prijs ik mij gelukkig met jullie aan mijn zijde en bovenal met de vriendschap die we hebben opgebouwd. We lachen wat af! Wat ooit begon met een meer-voor-mannen filmavond, die geleidelijk overging in een ingewikkelde boekbespreking met kipsaté (voor wat kortere duur), zijn het met name de memorabele avonden in Café Nol geweest die ons het meest bekoorden. Behalve dan die avond dat Wouter zijn laptop in de Nol rondging. Ik ben heel trots op jullie moedige besluit om na de opleiding tot psychiater, voor de wetenschap een onbepaalde tijd naar het buitenland te gaan (Wouter in Boston, Maarten in Kopenhagen). Het is fijn te merken dat dit er niet toe heeft geleid dat we minder intensief met elkaar optrekken, sterker: Wouter onze driedaagse vrij decadente maar onvergetelijke trip naar New York met Mart als jou getuige was onvergetelijk. En Maarten, wat hebben we achteraf gelachen om onze neurotische afweer tijdens de weekendtrip in Kopenhagen, de manier waarop we ons voorbereidden op de halve marathon. Nu we de smaak te pakken hebben staat de Halve van Egmond voor deur en, wie weet, daarna de Boston Marathon bij Wouter? ;)

Graag wil ik alle LASA-deelnemers van harte bedanken voor hun deelname aan de studie. Daarnaast het datamanagement- en veldwerkteam bestaande uit Jan, Marleen, Priyanta en Majogee. Allen, wat verzetten jullie een werk, het is een luxe dat de data zo goed georganiseerd zijn om direct mee aan de slag te kunnen. Beste Jan, ik zal het dollen van jou missen, je enthousiasme tijdens de LASA-uitjes (zoals het voortijdig wegschieten van een pijl op je LASA-collega's) en jouw voorliefde voor het wielrennen en Ajax. Jij en Erik samen haalden echter ook het slechtste in elkaar naar boven, zeker wanneer Liverpool weer had gespeeld. Jullie waren dan niet te houden. Uiteraard wil ik de vele LASA/EMGO/NESDO-onderzoekers bedanken, die ik ergens in de afgelopen jaren tijdens mijn onderzoektijd heb ontmoet, voor de leuke tijd: Almar, Wim, Tjalling, Joost, Nicole, Tessa, Sascha, Maaike, Lisa (2x), Najada, Judith, Ilse (2x) en Erik.

Tja Erik, "ik ben niet zo van de lunchpraat" zeiden we tegen elkaar als we om 12.30u acte de présence moesten geven. LASA is nogal van de tijd. Wij waren meer van het pingpongen, althans ik, jij meer voor spek en bonen. Wist je trouwens dat "Health and Place" een Impact Factor heeft van 3.0? Beste Erik, wat was/is het genieten als jij bij LASA aanwezig was/bent. Dank voor die bijzondere momenten samen, jouw humor en steun, jij was altijd op de hoogte en geïnteresseerd.

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Doordat ik de opleiding tot psychiater combineerde met promotieonderzoek, wisselde ik telkens een jaar onderzoek af met een jaar opleiding. Daardoor heb ik bij GGZ inGeest-VUmc ook veel mensen ontmoet met wie ik heb mogen samenwerken en die veel voor mij hebben betekend. Leden van de medische staf en opleidingsgroep, Gerthe Veen, Barbara Besier, Michiel de Leeuw, Nikander Ruhl, Leo Swaab, Caroline Sonnenberg en Annemieke Dols. Natuurlijk ook mijn mede-AIOS met wie ik heb samengewerkt of gefeest, Barbara, Koen, Josine, Noach, Wicher, Ruud, Frits, Mardien, Nadine, Flora, Angela (2x), Awinash en Berrie. In het bijzonder wil ik ook mijn intervisiegroep bedanken, Ellemijn en Marc (de stichters), Juul, Sjors, Anne-Suzanne en Evelien.

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als ik voor bepalende keuzes in het leven sta (en jouw goede smaak voor Whisky). Beste Chris, met jou ervaar ik dat evenzo, je bent een belangrijk persoon voor mij geworden, via onze vrouwen hebben we elkaar leren kennen. Enkele jaren geleden ben je naar jouw Heimat vertrokken, München, prachtig om te zien (en mee te maken) hoe goed je daar op je plek bent: niet alleen tijdens de Wiesn. Onze passie voor bergwandelen breid ik de komende jaren graag met je uit.

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Lieve papa en mama, ik ben heel trots op hoe jullie de eigen horizon hebben verbreed (en nog steeds doen) en wat mij is bijgebracht. Jullie zijn op vrij jonge leeftijd op eigen houtje een weg ingeslagen die niet makkelijk is, noch voorhanden lag, gezien het gezin van oorsprong. Door die ruimte te maken, hebben jullie voor ons/mij een weg vrijgemaakt waarin het vanzelfsprekend was om verder te studeren. Dank hiervoor. Pa, jij bent altijd een stimulerende factor geweest, ik vind het bewonderenswaardig dat presteren nooit een must voor jou was, maar een mooie bijkomstigheid bij datgene wat gewoon leuk is om te doen. Ma, wellicht minder op de hoogte van het inhoudelijke deel van mijn proefschrift, jij was niet minder betrokken. Regelmatig stuurde jij mij een selectie krantenartikelen met als noemer psychiatrie. Je onuitputtelijke energie en liefde is ongekend. Zo hielp je ons aan de start van het promotieonderzoek uit de brand door er bijna vier jaar lang voor Imre te zijn waarbij jij iedere week op en neer reisde van Leeuwarden naar Amsterdam en weer terug. Jij voelde je dan als vis in het water in de stad Amsterdam, prachtig. Met ons aanstaande vertrek naar Noord-Nederland zal er meer tijd zijn, ook voor onze kinderen om hun opa en oma te bezoeken.

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Amsterdam, bedankt!

Appendix

About the author

About the author

Hans Jeuring was born on April 28st, 1984 in Heerenveen. After finishing his pre-university training at the Piter Jelles College in Leeuwarden (2003), he studied medicine at the Faculty of Medical Sciences of the University of Groningen (BSc 2007, MSc 2010). During his study he participated as a congress board member of the International Student Congress of Medical Sciences in Groningen. From 2010 onwards he worked shortly as a senior house officer at GGZ inGeest in Amsterdam. In April 2011 until April 2017 he was a resident psychiatry at GGZ inGeest and the VU University Medical Center in Amsterdam. In October 2013 he started to combine his residency with a PhD program at the Department of Epidemiology and Biostatistics at the VU University Medical Center in Amsterdam. From April 2018 until April 2019 he worked as a psychiatrist in the Department of Hospital Psychiatry at the Medical Center Leeuwarden. Since April 2019 he works in the Department of Old Age Psychiatry at the University Center of Psychiatry within the University Medical Center Groningen. Hans lives in Amsterdam together with his partner Daphne van Vliet and their children, Imre and Ruby Rose.

Appendix

List of publications

List of publications

Jeuring, H.W., Huisman, M., Comijs, H.C., Stek, M.L., Beekman, A.T.F. (2016). The long-term outcome of subthreshold depression in later life. *Psychological Medicine,* Oct;46(13):2855-2865.

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Appendix

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